TOXICOLOGICAL PROFILE FOR CHLORODIBENZOFURANS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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UPDATE STATEMENT

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:

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and 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 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 revised list of the 275 most hazardous substances was published in the Federal Register on October 28, 1992 (57 FR 48801). 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); and October 17, 1991 (56 FR 52166).

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

(A) The examination, summary, and interpretation of available toxicological information and epidemiological evaluations on a 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.

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 is intended to succinctly characterize the toxicological 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, that describes in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to 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.

Foreword

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

This profile reflects 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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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

3. 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.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

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

1. Dr. Judith Bellin, Private Consultant, Washington, DC
2. Dr. Shane Que Hee, Department of Environmental Health Sciences, UCLA School of Public Health, Los Angeles, California
3. Dr. Stephen Safe, Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, Texas
4. Dr. Arnold Schecter, College of Medicine, Clinical Campus, Health Science Center/Syracuse,State University of New York, Binghamton, New York.

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

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

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

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about chlorinated dibenzofurans (CDFs) and to emphasize the human health effects that may result from exposure to them. The Environmental Protection Agency (EPA) has identified 1,350 hazardous waste sites as the most serious in the nation. These sites comprise the "National Priorities List" (NPL): Those sites which are targeted for long-term federal cleanup activities. CDFs have been found in at least 57 of the sites on the NPL. However, the number of NPL sites evaluated for CDFs is not known. As EPA evaluates more sites, the number of sites at which CDFs is found may increase. This information is important because exposure to CDFs may cause harmful health effects and because these sites are potential or actual sources of human exposure to CDFs.

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 substances containing the substance or by skin contact with it.

If you are exposed to substances such as CDFs, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, gender, nutritional status, family traits, life-style, and state of health.

1.1 WHAT ARE CDFs?

CDFs are a family of chemicals known as chlorinated dibenzofurans. These chemicals contain one to eight chlorine atoms attached to the carbon atoms of the parent chemical, dibenzofuran. The CDF family contains 135 individual compounds (known as congeners) with varying harmful health and environmental effects. Of these 135 compounds, those that

contain chlorine atoms at the 2,3,7,8-positions of the parent dibenzofuran molecule (see Section 3.1) are especially harmful. Other than for laboratory use of small amounts of CDFs for research and development purposes, these chemicals are not deliberately produced by industry. Most CDFs are produced in very small amounts as unwanted impurities of certain products and processes utilizing chlorinated compounds. Only a few of the 135 CDF compounds have been produced in large enough quantities so that their properties, such as color, smell, taste, and toxicity could be studied. The few CDF compounds that have been produced in those quantities are colorless solids. They do not dissolve in water very easily. There is no known use for these chemicals. You will find further information on the physical properties of these compounds in Chapter 3 of this profile. CDFs are often found in association with dibenzo-p-dioxins (CDDs), which cause similar toxic effects.

1.2 WHAT HAPPENS TO CDFs WHEN THEY ENTER THE ENVIRONMENT?

Small amounts of CDFs can enter the environment from a number of sources. Accidental fires or breakdowns involving capacitors, transformers, and other electrical equipment (e.g., fluorescent light fixtures) that contain polychlorinated biphenyls (PCBs) are known to release high levels of CDFs formed by thermal degradation. A fire involving a transformer containing PCBs contaminated the State Office Building in Binghamton, New York, with CDFs. Accidents of a different kind involving heated PCBs occurred in Japan (Yusho incident) and Taiwan (Yu-Cheng incident). These incidents involved exposure to CDFs-contaminated PCBs that were used as a heat exchanger fluid for processing rice oil and which accidentally leaked into the oil. CDFs are also produced as unwanted compounds during the manufacture of several chlorinated chemicals and consumer products, such as wood treatment chemicals, some metals, and paper products. When the waste water, sludge, or solids from these processes are released into waterways or soil in dumpsites, they become contaminated with CDFs. CDFs also enter into the environment from burning municipal and industrial waste in incinerators. The exhaust from cars that use leaded gasoline, which contains chlorine, releases small amounts of CDFs in the environment. Small amounts of CDFs may also enter into the environment from burning of coal, wood, or oil for home heating and

production of electricity. Many of these chemicals or processes that produce CDFs in the environment are either being slowly phased out or strictly controlled.

CDFs in air are present mostly as solid particles and to a much lesser extent as vapor. Some of the CDFs present in air return to the land and water by settling, snow, and rainwater. An amount of CDFs in the vapor phase is destroyed by reacting with certain chemical agents (called hydroxyl radicals) naturally present in the atmosphere. CDFs may remain in air for an average of more than 10 days depending on the CDF compound. Once in the air, CDFs can be carried long distances. They have been found in air and waters and at the bottom of lakes and rivers in areas far away from where they were released into the environment. CDFs tend to stick to suspended particles and settled particles in lakes and rivers and can remain at the bottom of lakes and rivers for several years. Sediment acts as a medium where CDFs that are present in air or water eventually settle. CDFs can build up in fish, and the amount of CDFs in fish can be tens of thousands times higher than the levels in water. The CDFs in water can get into birds or other animals and humans that eat fish containing CDFs. CDFs bind strongly to soil and are not likely to move from the surface soil into groundwater. In some instances, CDFs from some waste landfills may reach underground water. CDFs are more likely to move from soil to water or other soils by soil erosion and flooding. The breakdown or loss of CDFs in soil occurs over years, so CDFs remain in soil for years. Most CDFs found in plants are probably deposited by air. Cattle that eat plants on which CDFs have been deposited will build up some of the CDFs in their bodies. Some of the CDFs will enter the milk and meat of cattle. You will find more information about the fate and movement of CDFs in the environment in Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO CDFs?

CDFs are found at very low levels in the environment of industrial countries and at even lower levels in nonindustrial countries. People are exposed to very small levels of CDFs by breathing air, drinking water, and eating food, but most human exposure comes from food containing CDFs. The levels of CDFs in air are usually higher in city and suburb areas than in rural areas. The concentration of CDFs in city and suburb areas ranges from less than one

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femtogram (fg) (one quadrillionth of a gram, that is 1/100,000,000,000th of a gram) to a few picograms (pg) in a cubic meter (m^3) of air. The levels in rural air are usually so low that measurements are not possible. The levels of CDFs in most drinking waters are also below the level that can be measured. CDFs were found in drinking water of one of the 20 water supplies in New York State at a concentration of 3.4 parts of CDF in a quadrillion part of water. CDFs are not found in soils that have not been polluted. CDFs have been detected in the stack emissions and ash from certain industries and processes that are sources of these compounds in air at levels that are thousands of times higher than the levels in the air that we usually breathe. Once emitted in the air from stacks, CDFs are dispersed by the cleaner air and the level of CDFs drops substantially. Similarly, the levels of CDFs in waste waters from certain industries and in soil at dumpsites can be thousands to millions times higher than the levels found in clean water and soil.

Some products you use, such as paper towels, coffee filters, tampons, and milk cartons, can contain extremely low levels of CDFs. The intake of CDFs from these sources is very low. Since CDFs tend to concentrate in the fat, and milk contains fat, mother's milk can be a source of CDFs for babies. But considering the small amounts of CDFs in milk and the other beneficial effects of human milk to a baby and the length of time a baby uses mother's milk, scientists believe that mother's milk, on balance, is still beneficial to babies. Cow's milk and formula usually contain lower amounts of CDFs than human milk. Children playing in dumpsites may come in contact with CDFs through their skin and by eating dirt. It has been estimated that over 90% of the total daily intake of CDFs (on the order of a few pg per day) for the general adult population occurs from eating food containing them. The rest comes from air, consumer products, and drinking water. Meat and meat products, fish and fish products, and milk and milk products contribute equally to intake of CDFs from food, while intake from vegetable products contributes much less. Eating large amounts of fatty fish from water containing CDFs may increase your daily intake of CDFs from food.

People in certain occupations may be exposed to higher levels of CDFs than the general population. Exposure in the workplace occurs mostly by breathing air and touching substances that contain CDFs. Workers involved with cleaning up after transformer fires,

workers in the pulp and papermill industry, workers in municipal incinerators, and workers in sawmills may be exposed to higher levels of CDFs than the general population. Contact with CDFs at hazardous waste sites can happen when workers breathe air or touch soil containing CDFs. You will find more information about CDF exposure in Chapter 5 of this profile.

1.4 HOW CAN CDFs ENTER AND LEAVE MY BODY?

If you breathe air that contains CDFs, they can enter your body through your lungs and pass into the bloodstream, but we do not know how fast this occurs or how much of the CDFs will pass into the bloodstream. If you swallow food, water, or soil contaminated with CDFs, most of the CDFs will probably enter your body and pass from the stomach into the bloodstream, but we do not know how fast this occurs. If you touch soil containing CDFs, which might occur at a hazardous waste site, some of the CDFs will pass through your skin into the bloodstream, but we do not know how fast this occurs. Most commonly, CDFs enter your body when you eat food contaminated with CDFs, in particular fish and fish products, meat and meat products, and milk and milk products containing CDFs. Exposure from drinking water is less than that from food. For people living around waste sites and for people who work with or around other chemicals that produce CDFs when heated, skin contact with contaminated soil or breathing CDF vapors are the most likely ways CDFs will enter the body. Once CDFs are in your body, some may change into breakdown products called metabolites. We do not know whether these metabolites are harmful. Some metabolites and some unchanged CDFs may leave your body mainly in the feces and in very small amounts in the urine in a few days, but other unchanged CDFs may stay in your body and be stored for years in your body fat. CDFs build up in milk fat and can enter the bodies of infants through breast feeding. CDFs can also enter the bodies of unborn babies through the placenta. For more information on how CDFs can enter and leave your body, see Chapter 2.

1.5 HOW CAN CDFs AFFECT MY HEALTH?

Much of what we know about the health effects of CDFs comes from studies of accidental poisonings in Japan and Taiwan in the 1960s and 1970s where many people ate food cooked

in contaminated rice oil for several months. In both of these incidents, the rice oil was contaminated with PCBs that contained CDFs. The amounts of CDFs that these people accidentally ate were much higher than those normally found in your diet. Skin and eye irritations, especially severe acne, darkened skin color, and swollen eyelids with discharge, were the most obvious health effects of the CDF poisoning. However, these effects did not develop in some people until weeks or months after exposure and might not have occurred at all in other people. CDFs also caused vomiting and diarrhea, anemia (a blood disease), more frequent lung infections, numbness and other effects on the nervous system, and mild changes in the liver, but there were no permanent liver changes or definite liver damage in the people who accidentally ate the CDFs. The children born to the poisoned mothers also had acne and other skin irritations. Young children of these mothers also had some trouble learning, but we do not know if this effect was permanent. It is unknown whether these health effects were caused by CDFs alone or CDFs and PCBs in combination. We know nothing about the health of people who are exposed to low levels of CDFs by breathing, skin contact, or for long periods of time.

Many of the same health effects that occurred in the people accidentally exposed also occurred in experimental or laboratory animals that ate CDFs. Animals fed CDFs also had severe body weight loss, and their stomachs, livers, kidneys, and immune systems were seriously injured. Some fed high doses died. CDFs also caused birth defects and testicular damage in animals, but we do not know if CDFs make males or females infertile. Most of the effects in animals occurred after they ate large amounts of CDFs for short periods or smaller amounts of CDFs for several weeks or months. Nothing is known about the possible health effects in animals from eating CDFs over a lifetime. Only one study tested animals exposed to CDFs by skin contact. The health effects were similar to those that occurred in animals that ate CDFs. We do not know the possible health effects in animals of breathing in CDFs. The amounts of CDFs that caused health effects in animals were far greater than the levels normally found in the environment.

We do not definitely know if CDFs caused cancer in any of the accidentally poisoned people. There are no cancer studies in animals that ate or breathed CDFs. One study found that

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CDFs alone did not cause skin cancer in animals when they were applied to the skin for several months. However, when researchers applied another carcinogen to the animals' skin before applying CDFs, skin cancer developed. Although skin cancer developed in these animals, the Department of Health and Human Services, the International Agency for Research on Cancer, and the Environmental Protection Agency have not classified the carcinogenicity of CDFs.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CDFs?

There are tests to find out if CDFs are in blood, body fat, and breast milk; however, these are not routinely done. High levels of CDFs in these body fluids and in fat will show that you have been exposed to high levels of CDFs. However, these measurements cannot show the exact amount or type of CDFs you were exposed to or for how long you were exposed. These tests do not predict whether you will experience harmful health effects. Blood tests can detect recent exposures to CDFs, but are not always the easiest, safest, or best method. Fat biopsies (small amounts of fat taken with a needle and syringe) may be less traumatic to a small child or very sick person and more diagnostic than blood tests. Nearly everyone in the United States and other industrial countries has been exposed to CDFs because they are found throughout the environment, and nearly all people are likely to have some CDFs in their blood, fat, and breast milk. For more information on tests to determine whether you have been exposed to CDFs, please refer to Chapters 2 and 6.

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

There are no federal guidelines or recommendations for protecting human health from exposure to CDFs. CDFs are, however, listed as hazardous waste components by the EPA.

1.8 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, E-29
Atlanta, Georgia 30333
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of CDFs are indicated in Table 2.2.

CDFs are a class of structurally similar chlorinated hydrocarbons containing two benzene rings fused to a central furan ring (see chemical structure Section 3.1). Based on the number of chlorine substituents (one to eight) on the benzene rings, there are eight homologues of CDFs (monochlorinated through octachlorinated). Each homologous group contains one or more isomers. There are 135 possible CDF isomers, including 4 monochlorinated dibenzofurans (monoCDFs), 16 dichlorinated dibenzofurans (diCDFs), 28 trichlorinated dibenzofurans (triCDFs), 38 tetrachlorinated dibenzofurans (tetraCDFs), 28 pentachlorinated dibenzofurans (pentaCDFs), 16 hexachlorinated dibenzofurans (hexaCDFs), 4 heptachlorinated dibenzofurans (heptaCDFs) and 1 octachlorinated dibenzofuran (octaCDF). The term congener is used to refer to any one particular isomer. Mono-, di-, and trichlorinated CDFs are not considered in this profile.

Health effects have been evaluated in humans exposed to undefined mixtures of congeners of CDFs. Information regarding health effects in animals exposed to CDFs was located for the following congeners: 1,2,4,6,7,9-heptachlorodibenzofuran (1,2,4,6,7,9-heptaCDF); 1,2,3,4,6,8,9-heptachlorodibenzofuran (1,2,3,4,6,8,9-heptaCDF); 1,2,4,6,7,9-hexachlorodibenzofuran (1,2,4,6,7,9-hexaCDF); 1,2,3,4,7,8-hexachlorodibenzofuran (1,2,3,4,7,8-hexaCDF); 1,2,3,6,7,8-hexachlorodibenzofuran (1,2,3,6,7,8-hexaCDF); 1,2,3,4,6,7,8,9-octachlorodibenzofuran (1,2,3,4,6,7,8,9-

octaCDF); 2,3,4,7&pentachlorodibenzofuran (2,3,4,7-pentaCDF); 1,2,3,7,8-pentachlorodibenzofuran (1,2,3,7,8-pentaCDF); 1,2,3,4,8-pentachlorodibenzofuran (1,2,3,4,8-pentaCDF), 2,3,7,8-tetrachlorodibenzofuran (2,3,7,8-tetraCDF). Some of the animal studies used mixtures of isomers which are described in appropriate sections of the profile. Of all the CDF congeners, those containing chlorine in the 2,3,7,8 carbon positions, particularly 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF, have been most extensively studied in animals.

CDDs frequently occur with CDFs in the environment. Because of this and due to evidence of a common mechanism of action, total toxicity of a CDFKDD mixture involves both CDFs and CDDs. CDDs appear to usually, but not always, contribute more to total toxicity than CDFs. CDDs are evaluated in a separate ATSDR toxicological profile (ATSDR 1994).

2.2.1 Inhalation Exposure

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

2.2.1 .I 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 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to CDFs.

2.2.2 Oral Exposure

Much of the information that pertains to human health effects of CDFs comes from large numbers of people who consumed rice oil contaminated with PCBs heat exchange fluid in Japan in 1968 (Yusho incident) and Taiwan in 1979 (Yu-Cheng incident) (Chen and Hsu 1986; Kuratsune 1989; Kashimoto and Miyata 1986; Okumura 1984; Rogan 1989). The PCBs were heated in thermal heat exchangers before contamination occurred, and also during cooking, resulting in the production of relatively high concentrations of CDFs and polychlorinated quaterphenyl (PCQ) impurities by thermal degradation. Yusho involved at least 1,854 victims exposed over ≈l0 months, and Yu-Cheng involved at least 2,061 victims exposed over ≈9 months (Chen et al. 1985b; Hsu et al. 1984; Kuratsune 1989; Rogan 1989). The concentrations of PCBs and PCQs in the rice oils were l00- to 500-fold greater than the CDFs. Because there are no data on human health effects of CDFs alone and little is known about the interactive effects of CDFs and PCBs and other components of the contaminated rice oils mixtures, the health effects in Yusho and Yu-Cheng victims cannot be attributed solely to CDFs. However, CDFs are generally considered to be the main causal agent based predominantly on comparisons with Japanese workers with higher PCB blood levels who had few or none of the symptoms present in the rice oil poisonings, decreasing serum levels of PCBs in victims with persisting health effects, induction of Yusho health effects in animals exposed to reconstituted mixtures of CDF congeners similar to those in Yusho oils, but not by exposure to PCBs or PCQs alone, and comparative toxicity evaluations of PCB and CDF congeners in unheated source mixtures, contaminated rice oil, and tissues of victims (Bandiera et al. 1984a; Kunita et al. 1984; Masuda and Yoshimura 1984; Ryan et al. 1990; Safe 1990; Takayama et al. 1991; Tanabe et al. 1989). In general, clinical severity of signs and symptoms was closely related to the total amount of oil consumed, but not to the amount consumed per kg body weight per day (Hayabuchi et al. 1979; Kuratsune 1989). Concentrations of CDFs in the Yu-Cheng oil were much lower than in the Yusho oil, and intake of Yu-Cheng oil was believed to be much higher than for Yusho oil (Chen et al. 1985b). This resulted in very similar estimated average total intakes of PCBs, CDFs, and PCQs of 633, 3.3, and 596 mg, respectively, for Yusho (Hayabuchi et al. 1979), and 973, 3.8, and 586 mg, respectively, for Yu-Cheng (Chen et al. 1985b). Based on the Yusho intake, the average daily amount of CDFs ingested per kg body weight was 0.9 μg/kg/day (Hayabuchi et al. 1979). Of more than 40 CDF congeners present in Yusho and Yu-Cheng oils, the two major congeners that accumulated in the victims are 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF. Contributions of other 2,3,7,8-chlorine substituted CDF congeners to the toxic effects are not

considered to be substantial since they were not present in significant amounts in the rice oils, were not detectably accumulated in human tissues, and/or were of lower potency (Ryan et al. 1990).

2.2.2.1 Death

There was no significant increase in the number of deaths from nonmalignancies or all causes in 887 male or 874 female Yusho victims (Kuratsune et al. 1987). As discussed in Section 2.2.2.8, some increased mortality from malignant neoplasms was observed. Twenty-four deaths were observed in 2,061 cases of Yu-Cheng poisoning identified by the end of 1983 (Hsu et al. 1985). The number of expected deaths was not reported, but half of the deaths were attributed to nonmalignant or malignant liver disease (see Section 2.2.2.2). No more recent comprehensive data on Yu-Cheng deaths are available (Rogan 1989). Deaths in infants born to mothers with Yusho and Yu-Cheng exposure are discussed in Section 2.2.2.6.

Information on lethality of CDFs in animals following acute oral exposure is available for 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF administered by gavage. Due to a long latent period for the onset of toxicity, reliable determination of toxic dose requires a sufficient observation period (typically 30 days in rodents). An LD_{50} of 916 μg/kg has been estimated for 2,3,4,7,8-pentaCDF in male Fischer-344 rats (Brewster et al. 1988). A CDF mixture containing 88% 2,3,7,8-tetraCDF (remainder primarily an unidentified pentaCDF) did not cause death in C57Bl/6Fh mice when tested at doses ≤6,000 μg/kg (Moore et al. 1976). Single 2,3,7,8-tetraCDF doses of 1,000 μg/kg and higher, but not 500 μg/kg, were lethal in rhesus monkeys observed for 60 days, but small numbers of animals (two to four) were tested (Moore et al. 1979). The Hartley guinea pig is the most sensitive of the species tested as indicated by lethality following single doses of 2,3,7,8-tetraCDF or 2,3,4,7,8-pentaCDF as low as 10 μg/kg (Ioannou et al. 1983; Moore et al. 1976, 1979).

Intermediate duration studies have evaluated the lethality of 2,3,7,8-tetraCDF and various pentaCDF congeners in animals. Although limited by small numbers of animals (three to eight per dosage), gavage studies with 2,3,7,8-tetraCDF indicate that Hartley guinea pigs are much more sensitive than C57B1/6Fh mice (Ioannou et al. 1983; Moore et al. 1979). Weekly doses of 1 μg/kg for 6-14 weeks produced 30-70% mortality in guinea pigs, whereas 22 doses of 300 μg/kg in 30 days caused no deaths in mice observed for an additional 30 days (Luster et al. 1979a, 1979b). One of three monkeys died following dietary administration of 2,3,7,8-tetraCDF in estimated dosages of 2.1 μg/kg/day for

2 months or 0.21 μg/kg/day for 6 months (McNulty et al. 1981). Dietary administration of 10 pg 2,3,4,7,8-pentaCDF/kg/day for 13 weeks caused >90% mortality in 1va:SIV 50 (SD) rats (Pluess et al. 1988a; Poiger et al. 1989). This CDF was more toxic than the 1,2,3,7,8-penta-, 1,2,3,4,8-pentaCDF and 1,2,3,6,7,-hexaCDF congeners, which caused no deaths when similarly administered at dosages of ≤10, ≤300, and ≤10 μg/kg/day, respectively (Pleuss et al. 1988; Poiger et al. 1989).

No studies were located regarding lethality in animals after chronic oral exposure to CDFs.

The existing lethality data indicate that congeners substituted in the 2,3,7,8-positions, particularly 2,3,4,7,8-pentaCDF and 2,3,7,8-tetraCDF, are the most toxic congeners tested. There is a marked species variation in sensitivity, with the guinea pig and monkey being particularly sensitive, although this may differ for other end points. Single and repeated doses were extremely toxic, causing death at levels as low as 10 μg/kg and 0.2-l μg/kg/day, respectively. A wasting syndrome was the major toxic effect at lethal doses in most species (see Section 2.2.2.2), but this may not be the only cause of death.

The LD_{50} value and reliable LOAEL values for death in each species and acute- and intermediate-Duration categories for each congener are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.2.2 Systemic Effects

The highest NOAEL values and all reliable representative LOAEL values for each systemic effect in each species and acute- and intermediate-duration categories for each congener tested are recorded in Table 2- 1 and plotted in Figure 2-l.

Respiratory Effects. Clinical observations strongly suggest that Yusho and Yu-Cheng patients experienced frequent or more severe respiratory infections (Kuratsune 1989; Rogan 1989). Chronic bronchitis accompanied by persistent cough and sputum production was observed in 40-50% of some examined patients, with symptoms gradually improving during 5-10 years following onset (Nakanishi et al. 1985; Shigematsu et al. 1971, 1977). Physical findings differed from those in usual bronchitis in that many nonsmokers showed no crackles and some showed wheezes without radiologic, physiologic, or immunologic evidence of bronchial asthma or pulmonary emphysema (Nakanishi et al. 1985; Shigematsu et al. 1971). Information on immune status in Yusho and Yu-Cheng patients is discussed in Section 2.2.2.3.

TABLE 2-1. Levels of Significant Exposure to CDFs - Oral

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
ACUTE EXPOSURE									
Death									
1	Rat	(GO)	1 d 1x/d				916 (LD50)	Brewster et al. 1988	penta$_1$
2	Gn pig	(GO)	1 d 1x/d				10 (100% mortality)	Moore et al. 1979	penta$_1$
3	Gn pig	(GO)	1 d 1x/d				10 (100% mortality)	Moore et al. 1979	tetra
4	Monkey	(GO)	1 d 1x/d				1000 (50% mortality)	Moore et al. 1979	tetra
Systemic									
5	Rat	(GO)	1 d 1x/d	Resp	2000			Brewster et al. 1988	penta$_1$
				Cardio		500 (nail hemorrhages)			
				Gastro	250	500 (epithelial hyperplasia of nonglandular stomach)			
				Hemato		100 (decreased hemoglobin, MCHC, MCV)			
				Hepatic		100 (lipid accumulation, increased serum cholesterol)			
				Renal	1000	2000 (64% increased BUN in moribund animals, 34% increased relative kidney weight)			
				Other	250	500 (17% body weight loss)			

TABLE 2-1. Levels of Significant Exposure to CDFs - Oral (*continued*)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
6	Rat	(GO)	1 d 1x/d	Hepatic	40			Doyle and Fries 1986	$hexa_1$
7	Rat	(GO)	1 d 1x/d	Hepatic	40			Doyle and Fries 1986	octa
8	Rat	(GO)	1 d 1x/d	Hepatic	40			Doyle and Fries 1986	tetra
9	Rat	(GO)	1 d 1x/d	Hepatic Other (body weight)	53 53			Ahlborg et al. 1989	$penta_1$
10	Rat	(GO)	1 d 1x/d	Hepatic	40			Doyle and Fries 1986	$hepta_1$ $hepta_2$
11	Rat	(GO)	1 d 1x/d	Hepatic	40			Doyle and Fries 1986	$penta_1$
12	Gn pig	(GO)	1 d 1x/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc Other	15 15 15 15 1 15 15	5 (reduced muscle mass) 10 (epithelial hyperplasia of kidney, ureter and bladder)	10 (50% body weight loss, adrenal hemorrhage)	Moore et al. 1979	tetra

TABLE 2-1. Levels of Significant Exposure to CDFs - Oral (*continued*)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
13	Gn pig	(GO)	1 d 1x/d	Resp	30			Moore et al. 1979	penta$_1$
				Cardio	30				
				Gastro	30				
				Hemato	30				
				Musc/skel	1	3 (reduced muscle mass)			
				Hepatic	30				
				Renal		10 (epithelial hyperplasia of kidney, ureter and bladder)			
				Derm/oc	30				
				Other			10 (adrenal hemorrhage)		
14	Mouse	(GO)	1 d 1x/d	Resp	6000			Moore et al. 1976, 1979	tetra
				Cardio	6000				
				Gastro	6000				
				Musc/skel	6000				
				Renal	6000				
				Derm/oc	6000				
15	Monkey	(GO)	1 d 1x/d	Gastro	500		1000 (hemorrhage and ulcers)	Moore et al. 1979	tetra
				Hemato			500 (anemia, lymphopenia, neutrophilia)		
				Hepatic	500	1000 (increased SGOT, gall bladder and bile duct hypertrophy)			
				Renal	500	1000 (increased BUN)			
				Derm/oc			500 (facial edema, occluded or dilated meibomian, ceruminous and sebaceous glands, eyelash and nail loss, epidermal hyperkeratosis)		
				Other			500 (moderate to severe body fat loss)		

TABLE 2-1. Levels of Significant Exposure to CDFs - Oral (*continued*)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
Immunological									
16	Rat	(GO)	1 d 1x/d			100 (30% decreased thymus weight)	500 (thymic atrophy)	Brewster et al. 1988	$penta_1$
17	Gn pig	(GO)	1 d 1x/d			3[b] (mild thymic lymphoid hypoplasia)	10 (thymic atrophy)	Moore et al. 1979	$penta_1$
18	Gn pig	(GO)	1 d 1x/d			5 (mild thymic lymphoid hypo-plasia)	10 (thymic atrophy)	Moore et al. 1979	tetra
19	Mouse	(GO)	once			208 (ED50 for decreased antibody response to SRBC)		Kerkvliet et al. 1985	$hepta_3$
20	Mouse	(GO)	1 d 1x/d		6000			Moore et al. 1979	tetra
21	Monkey	(GO)	1 d 1x/d				1000 (thymic atrophy)	Moore et al. 1979	tetra
Developmental									
22	Rat	(GO)	1 d Gd8,10 or 12 1x/d			30 (decreased fetal body weight)	100 (increased fetal mortality)	Couture et al. 1989	$penta_1$
23	Rat	(GO)	Gd16 1x/d		0.5	2 (14% decreased relative neonatal thymus weight)		Madsen and Larsen 1989	$penta_1$
24	Mouse	(GO)	4 d Gd10-13 1x/d				100 (hydronephrosis)	Birnbaum et al. 1987b	$hexa_2$
25	Mouse	(GO)	4 d Gd10-13 1x/d				5 (hydronephrosis)	Birnbaum et al. 1987b	$penta_1$

TABLE 2-1. Levels of Significant Exposure to CDFs - Oral (*continued*)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
26	Mouse	(GO)	1 d Gd10 1x/d				250 (fetal mortality, hydronephrosis)	Weber et al. 1984	tetra
27	Mouse	(GO)	4 d Gd10-13 1x/d				10 (hydronephrosis)	Weber et al. 1984	tetra
28	Mouse	(GO)	4 d Gd10-13 1x/d		10		30 (hydronephrosis)	Birnbaum et al. 1987a	$penta_2$
29	Mouse	(GO)	4 d Gd10-13 1x/d		3		10 (hydronephrosis)	Birnbaum et al. 1987a	$penta_1$
30	Mouse	(GO)	4 d Gd10-13 1x/d				100 (hydronephrosis, cleft palate)	Birnbaum et al. 1987a	$hexa_2$
Reproductive									
31	Mouse	(GO)	4 d Gd 10-13 1x/d				80 (hemorhagic lesions in placenta)	Khera 1992	$penta_1$
32	Rat	(GO)	1 d 1x/d		2000			Brewster et al. 1988	$penta_1$
33	Gn pig	(GO)	1 d 1x/d			5 (hypocellularity of seminiferous tubules)		Moore et al. 1979	tetra
34	Gn pig	(GO)	1 d 1x/d			3 (hypocellularity of seminiferous tubules)		Moore et al. 1979	$penta_1$
INTERMEDIATE EXPOSURE									
Death									
35	Rat	(F)	13 wk				10 (92% mortality)	Pluess et al. 1988a; Poiger et al. 1989	$penta_1$

TABLE 2-1. Levels of Significant Exposure to CDFs - Oral (*continued*)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
36	Gn pig	(GO)	6 wk 1d/wk 1x/d				1 (30% mortality)	Luster et al. 1979a, 1979b	tetra
37	Monkey	(F)	2 mo				2.1 (33% mortality)	McNulty et al. 1981	tetra
38	Monkey	(F)	6 mo				0.21 (33% mortality)	McNulty et al. 1981	tetra
Systemic									
39	Rat	(F)	4 wk	Hemato			50 (hemolytic anemia)	Oishi and Hiraga 1978	$mixture_1$
				Hepatic		50 (porphyria)			
40	Rat	(F)	13 wk	Cardio	300			Pluess et al. 1988b; Poiger et al. 1989	$penta_3$
				Hemato	300				
				Hepatic	300				
				Renal	300				
				Other	300				
41	Rat	(F)	13 wk	Cardio	10			Pluess et al. 1988a; Poiger et al. 1989	$penta_1$
				Hemato	10				
				Hepatic		0.1[c] (increased serum bilirubin, decreased serum triglycerides)			
				Renal	10				
				Other	0.1	1 (11% decreased body weight gain)	10 (47-54% body weight loss)		
42	Rat	(F)	13 wk	Cardio	10			Pluess et al. 1988b; Poiger et al. 1989	$penta_2$
				Hemato	10				
				Hepatic	1	10 (increased liver weight, vacuolization with lipid accumulation, single cell necrosis)			
				Renal	10				
				Other	1	10 (6.5-11% decreased body weight)			

TABLE 2-1. Levels of Significant Exposure to CDFs - Oral (*continued*)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
43	Rat	(F)	13 wk	Cardio	10			Pluess et al. 1988b; Poiger et al. 1989	$hexa_3$
				Hemato	10				
				Hepatic	0.1	1 (increase liver weight, vacuolization with lipid accumulation, single cell necrosis)			
				Renal	10				
				Other	1	10 (14-20% decreased body weight gain)			
44	Rat	(F)	4 wk	Cardio	960			Oishi et al. 1978	$mixture_1$
				Hemato		97 (decreased hemoglobin, hematocrit and MCV, increased MCHC)			
				Hepatic		97 (increased liver weight and lipid content)			
				Renal	960				
				Derm/oc	97		960 (chloracne)		
				Other		97 (15% decreased body weight gain)			
45	Gn pig	(GO)	6 wk 1d/wk 1x/d	Hemato	1			Luster et al. 1979a, 1979b	tetra
				Other	1				
46	Mouse	(GO)	30 d 22 doses 1x/d	Hemato			300 (37% decreased total leukocytes)	Moore et al. 1979	tetra
				Hepatic		30 (25% increased relative liver weight)			
				Other (body weight, clinical signs)	300				

TABLE 2-1. Levels of Significant Exposure to CDFs - Oral (*continued*)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
47	Monkey	(F)	2 mo	Gastro		2.1 (intramucosal cysts)		McNulty et al. 1981	tetra
				Hemato	2.1				
				Hepatic		2.1 (altered bile duct epithelium)			
				Derm/oc			2.1 (periorbital edema, facial and body hair and nail loss, absent sebaceous glands)		
48	Monkey	(F)	6 mo	Gastro		0.21 (mucosal metaplasia)		McNulty et al. 1981	tetra
				Hemato	0.21				
				Hepatic		0.21 (altered bile duct epithelium)			
				Derm/oc			0.21 (periorbital edema, meibomian gland enlargement, partial sebaceous gland atrophy, *hyperkeratotic* nail beds)		
Immunological									
49	Rat	(F)	13 wk		300			Pluess et al. 1988b; Poiger et al. 1989	$penta_3$
50	Rat	(F)	13 wk		0.1	1 (decreased thymus weight)	10 (thymic atrophy)	Pluess et al. 1988b; Poiger et al. 1989	$hexa_3$
51	Rat	(F)	13 wk			0.1 (decreased thymus weight)	1 (thymic atrophy)	Pluess et al. 1988a; Poiger et al. 1989	$penta_1$
52	Rat	(F)	13 wk		1	10 (decreased thymus weight)		Pluess et al. 1988b; Poiger et al. 1989	$penta_2$

TABLE 2-1. Levels of Significant Exposure to CDFs - Oral (*continued*)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
53	Rat	(F)	4 wk			97 (decreased thymus weight)		Oishi et al. 1978	$mixture_1$
54	Gn pig	(GO)	6 wk 1d/wk 1x/d		0.17		0.5 (thymic atrophy, macrophage inhibition)	Luster et al. 1979a, 1979b	tetra
55	Mouse	(GO)	4 wk 1d/wk 1x/d		10	100 (decreased thymus weight)		Oishi and Hiraga 1980	$mixture_2$
56	Mouse	(GO)	30 d 22 doses 1x/d			300 (17% decreased thymus weight)		Moore et al. 1979	tetra
57	Monkey	(F)	6 mo				0.21 (thymic atrophy)	McNulty et al. 1981	tetra
58	Monkey	(F)	2 mo				2.1 (thymic atrophy)	McNulty et al. 1981	tetra
Reproductive									
59	Rat	(F)	13 wk		10			Pluess et al. 1988b; Poiger et al. 1989	$hexa_3$
60	Rat	(F)	4 wk		97	960 (decreased relative seminal vesicle weight and testosterone concentration in testes)		Oishi et al. 1978	$mixture_1$
61	Rat	(F)	13 wk		10			Pluess et al. 1988b; Poiger et al. 1989	$penta_2$
62	Rat	(F)	13 wk		300			Pluess et al. 1988b; Poiger et al. 1989	$penta_3$

TABLE 2-1. Levels of Significant Exposure to CDFs - Oral (continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
63	Rat	(F)	13 wk		10			Pluess et al. 1988a; Poiger et al. 1989	$penta_1$

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an acute oral Minimal Risk Level (MRL) of 0.001 µg/kg/day for 2,3,4,7,8-pentaCDF; dose divided by an uncertainty factor of 1,000 (10 for extrapolation from animals to humans, 10 for human variability, 10 for use of a LOAEL) and by a modifying factor of 3 to adjust for lack of neurological studies in animals.
[c]Used to derive an intermediate oral MRL of 0.00003 µg/kg/day for 2,3,4,7,8-pentaCDF; dose divided by an uncertainty factor of 1,000 (10 for extrapolation from animals to humans, 10 for human variability, 10 for use of a LOAEL) and by a modifying factor of 3 to adjust for lack of neurological studies in animals.

BUN = blood urea nitrogen; Cardio = cardiovascular; CDFs = chlorinated dibenzofurans; d = day(s); Derm/oc = dermal/ocular; (F) = feed; Gastro = gastrointestinal; Gd = gestation day; Gn pig = guinea pig; (GO) = gavage-oil; Hemato = hematological; LD50 = lethal dose; 50% kill; LOAEL = lowest-observed-adverse-effect level; MCHC = mean corpuscular hemoglobin concentrations; MCV = mean corpuscular volume; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; SGOT = serum oxaloacetic transaminase; wk = week(s); x = times

$hepta_1$ = 1,2,3,4,6,7,9-heptachlorodibenzofuran
$hepta_2$ = 1,2,3,4,6,8,9-heptachlorodibenzofuran
$hepta_3$ = 1,2,3,4,6,7,8-heptachlorodibenzofuran
$hexa_1$ = 1,2,4,6,7,9-hexachlorodibenzofuran
$hexa_2$ = 1,2,3,4,7,8-hexachlorodibenzofuran
$hexa_3$ = 1,2,3,6,7,8-hexachlorodibenzofuran
$mixture_1$ = synthesized mixture containing 2 tetraCDFs, 4 pentaCDFs, and 4 hexaCDFs (specific congeners not reported but average chlorine number is 4.7)
$mixture_2$ = CDF mixture containing 88% pentaCDFs and 12% tetraCDFs (specific congeners not reported)
octa = 1,2,3,4,6,7,8,9-octachlorodibenzofuran
$penta_1$ = 2,3,4,7,8-pentachlorodibenzofuran
$penta_2$ = 1,2,3,7,8-pentachlorodibenzofuran
$penta_3$ = 1,2,3,4,8-pentachlorodibenzofuran
tetra = 2,3,7,8-tetrachlorodibenzofuran

FIGURE 2-1. Levels of Significant Exposure to CDFs - Oral

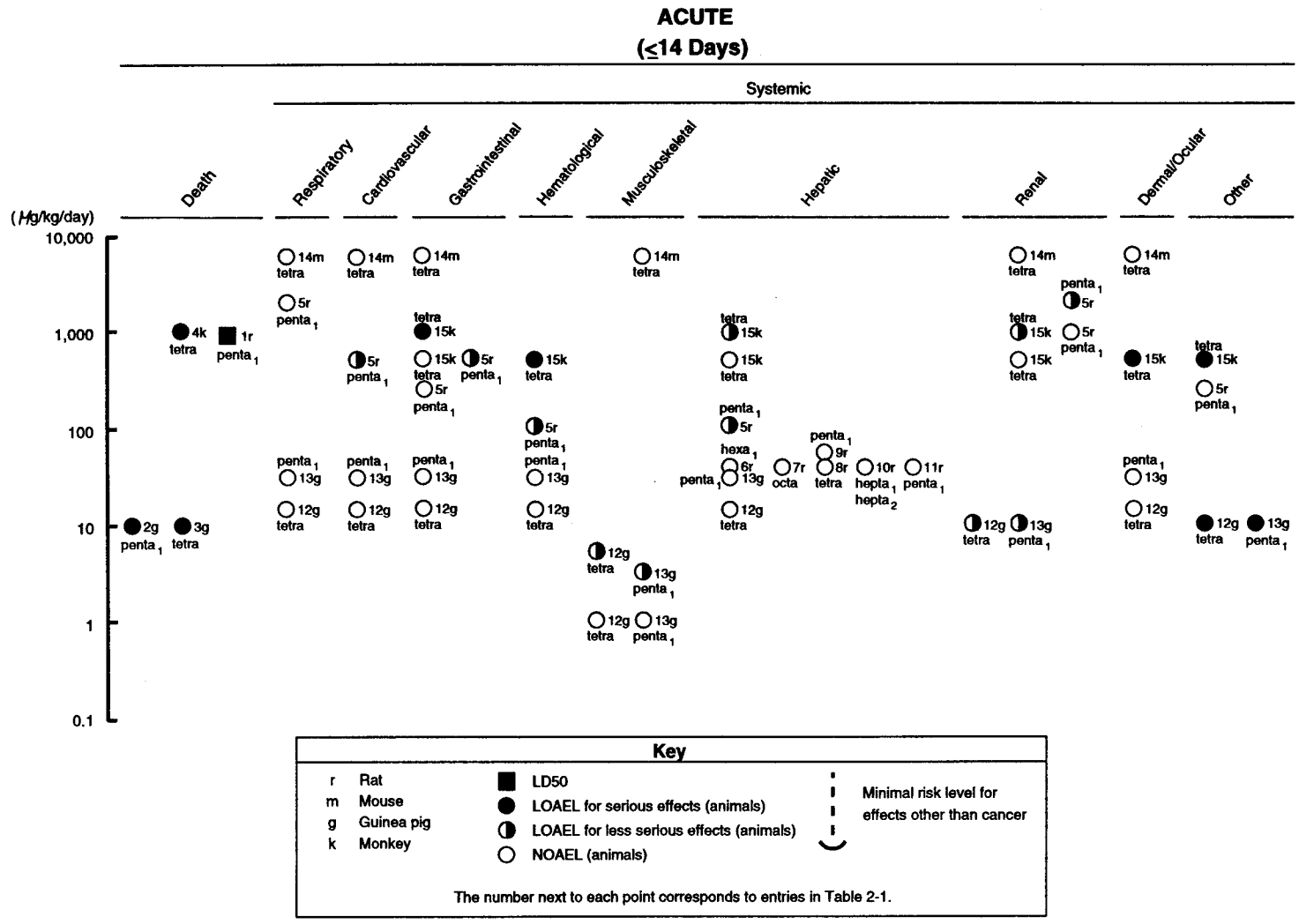


FIGURE 2-1. Levels of Significant Exposure to CDFs - Oral *(continued)*

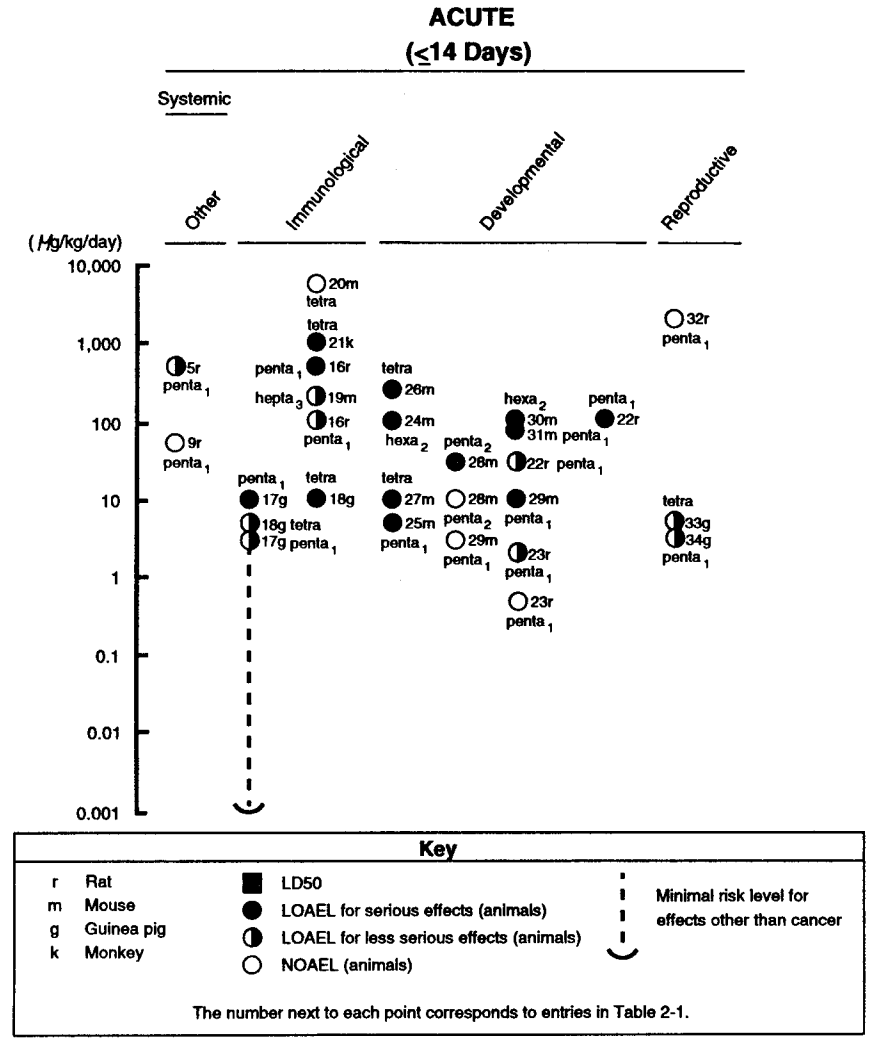


FIGURE 2-1. Levels of Significant Exposure to CDFs - Oral *(continued)*

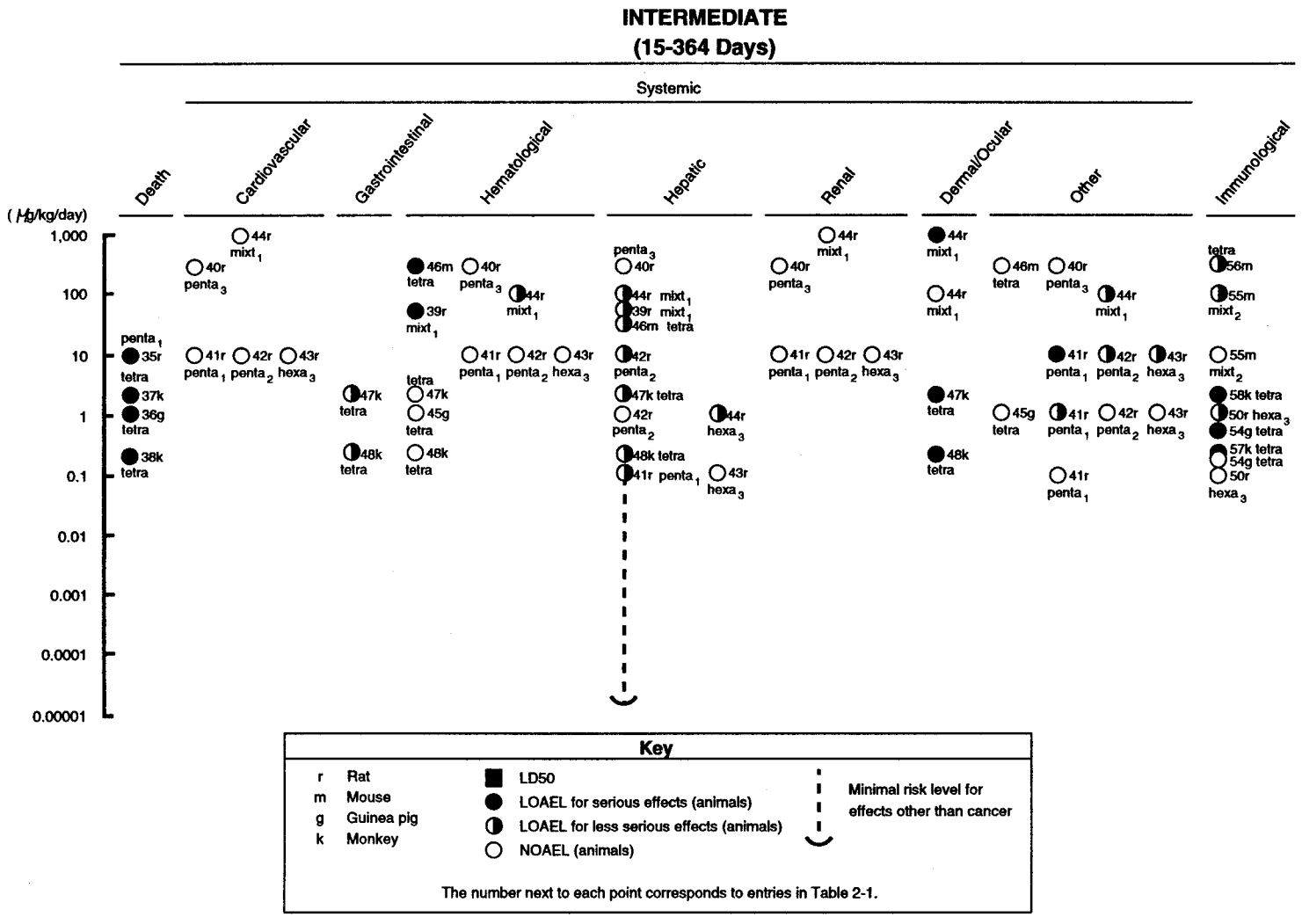
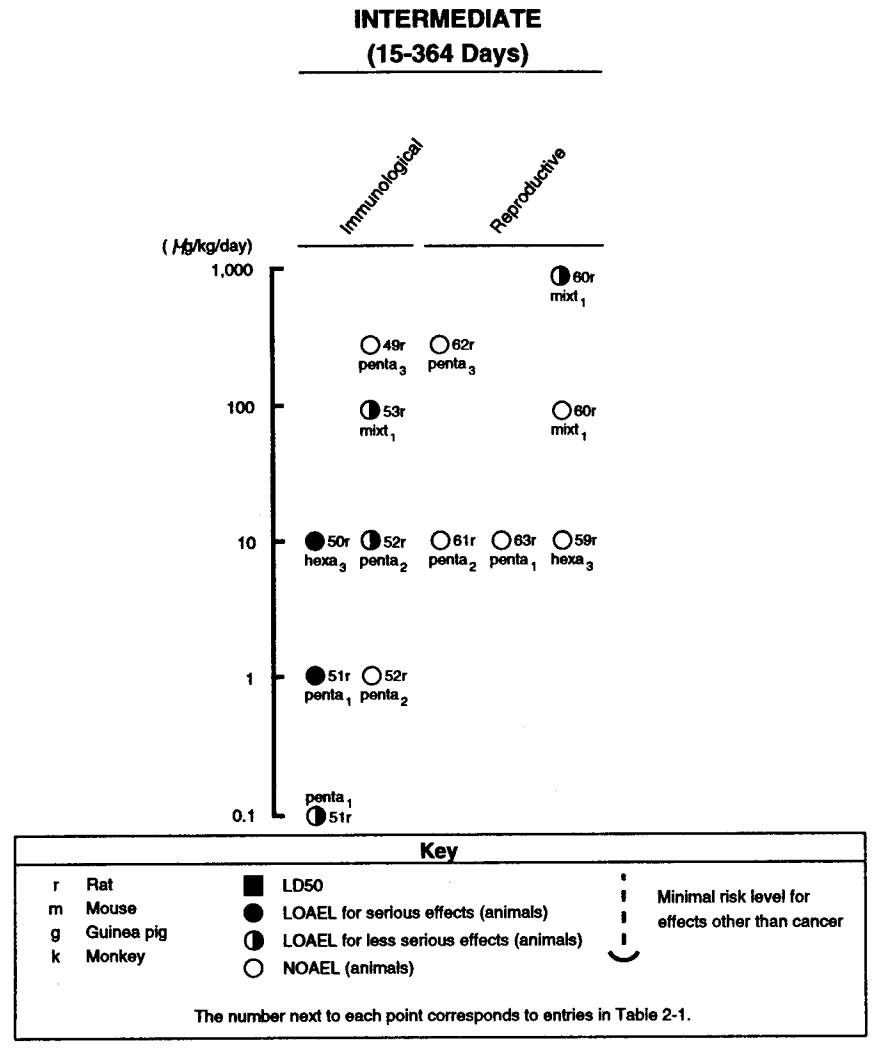


FIGURE 2-1. Levels of Significant Exposure to CDFs - Oral *(continued)*



2. HEALTH EFFECTS

No histological alterations were observed in the trachea or lungs of Hartley guinea pigs that were administered a single, nonlethal, gavage dose of ≤5 μg/kg 2,3,7,8-tetraCDF or ≤3 μg/kg 2,3,4,7,8-pentaCDF, in guinea pigs that were similarly treated with single, lethal doses ≤15 ug/kg 2,3,7,8-tetraCDF or 30 μg/kg 2,3,4,7,8-pentaCDF, or in C57B1/6Fh mice that were similarly treated with nonlethal doses ≤6,000 μg/kg 2,3,7,8-tetraCDF (Moore et al. 1979). Fischer-344 rats that were administered a lethal gavage dose of 2,000 μg/kg 2,3,4,7,8-pentaCDF showed no pulmonary histological changes (Brewster et al. 1988). The animals that received the nonlethal doses were examined after 30 days of observation.

No studies were located regarding respiratory effects in animals after intermediate or chronic duration oral exposure to CDFs.

The Yusho and Yu-Cheng data provide evidence that CDFs-induced bronchitis and related respiratory effects in humans. There is no evidence of pulmonary histological changes in animals exposed to single doses of CDFs, but longer term studies have not been performed, nonhuman primates were not tested, and only two congeners were evaluated (2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to CDFs.

No histological alterations were observed in the heart of Hartley guinea pigs that were administered a single nonlethal gavage dose of ≤5 μg/kg 2,3,7,8-tetraCDF or ≤3 μg/kg 2,3,4,7,8-pentaCDF, in guinea pigs that were similarly treated with single, lethal doses ≤15 μg/kg 2,3,7,8-tetraCDF or 30 μg/kg 2,3,4,7,8-pentaCDF, or in C57B1/6Fh mice that were similarly treated with nonlethal doses of ≤6,000 μg/kg 2,3,7,8-tetraCDF (Moore et al. 1979). The animals that received nonlethal doses were examined after 30 days of observation. Hemorrhages under the nails were observed in 4 of 13 Fischer-344 rats that died following a single, lethal gavage dose of 2,3,4,7,8-pentaCDF (Brewster et al. 1988), but it is unclear if the lowest lethal dose (500 μg/kg) is the LOAEL for this effect. Hemorrhages also were observed in the stomach of monkeys and adrenal of guinea pigs given lethal oral doses of 2,3,7,8-tetraCDF and/or 2,3,4,7,8-pentaCDF (Moore et al. 1979) (see Gastrointestinal Effects and Other Systemic Effects).

2. HEALTH EFFECTS

No histological alterations were observed in the heart of 1va:SIV 50 (SD) rats that were administered dietary dosages of ≤10 μg/kg/day 2,3,4,7,8-pentaCDF, 1,2,3,7,8-pentaCDF or 1,2,3,6,7,8-hexaCDF, or ≤300 μg/kg/day 1,2,3,4,8-pentaCDF, for 13 weeks (Pluess et al. 1988a, 1988b; Poiger et al. 1989). Dietary exposure to an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks caused increased relative heart weight at ≥97 μg/kg/day and decreased absolute heart weight at 960 μg/kg/day in Sprague-Dawley rats, but histology was not evaluated (Oishi et al. 1978). The increased relative heart weight is likely due to concurrent lower body weight (see Other System Effects). No studies were located regarding cardiovascular effects in animals after chronic duration oral exposure to CDFs.

The animal studies with 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF provide some evidence that CDFs can induce hemorrhagic effects at acute lethal doses, but studies of these and other 2,3,7,8-substituted CDF congeners give no indication of altered cardiac histology after acute or intermediate duration exposure. No differences are apparent among the rodent species tested and effects of CDFs on cardiac function have not been evaluated.

Gastrointestinal Effects. Early symptoms in 89 male and 100 female Yusho patients included vomiting (23.6% and 28% frequencies) and diarrhea (19.1% and 17%) (Kuratsune 1989). Additional information on possible gastrointestinal effect of CDFs in humans was not located.

No histological alterations were observed in the esophagus, stomach, or intestine of Hartley guinea pigs that were administered a single, nonlethal, gavage dose of ≤5 μg/kg 2,3,7,8-tetraCDF or ≤3 μg/kg 2,3,4,7,8-pentaCDF, in guinea pigs that were similarly treated with single lethal doses ≤15 μg/kg 2,3,7,8-tetraCDF or 30 μg/kg 2,3,4,7,8-pentaCDF, or in C57B1/6Fh mice that were similarly treated with nonlethal doses of ≤6,000 μg/kg 2,3,7,8-tetraCDF (Moore et al. 1979). The animals that received nonlethal doses were examined after 30 days of observation. In contrast, epithelial hyperplasia of the nonglandular stomach, characterized by acanthosis and hyperkeratosis, was observed in Fischer-344 rats that were administered a single, near-lethal, gavage dose of 500 μg/kg 2,3,4,7,8-pentaCDF and observed for 35 days, but not at 250 μg/kg and lower doses (Brewster et al. 1988). Similarly, gastric lesions developed in rhesus monkeys that were administered a single lethal dose of 1,000 μg/kg 2,3,7,8-tetraCDF and observed for 60 days, but not at a nonlethal dose of 500 μg/kg (Moore et al. 1979). Effects including hyperemia, scattered petechial hemorrhage, focal ulceration, and mucosal

cysts in the fundic and duodenal areas of the stomach and small intestine occurred in three of six monkeys.

Gastric mucosal changes occurred in rhesus monkeys treated with dietary 2,3,7-tetraCDF in intermediate duration studies (McNulty et al. 1981). Mucous metaplasia of the gastric mucosa was found in a monkey that died from ingestion of 0.21 μg/kg/day for 6 months. Intramucosal cysts and cystic growth of mucous glands in the submucosa occurred in the stomach of another monkey that died from ingestion of 2.1 μg/kg/day for 2 months. Although only one animal per dosage was evaluated, these findings are consistent with those observed in the acute study with monkeys and considered to be compound-related, No studies were located regarding gastrointestinal effects in animals after chronic duration oral exposure to CDFs.

The animal studies indicate that the gastric mucosa is a target of CDFs in monkeys and rats at nearlethal and lethal doses and suggest that guinea pigs and mice are less sensitive rodent species. Only a few studies were performed, however, and congeners other than 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF were not tested.

Hematological Effects. Mild normocytic anemia and leukocytosis are fairly consistent findings in Yu-Cheng patients (Rogan 1989).

Various hematological alterations have been observed in animals treated with 2,3,78-substituted CDF congeners, but decreased hemoglobin appears to be the only consistent finding. In acute duration studies, Fischer-344 rats that were administered single gavage doses of ≥100 μg/kg 2,3,4,78-pentaCDF and evaluated 7-21 days following treatment showed dose-related decreased hemoglobin concentration, mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) (Brewster et al. 1988). There were no changes in mean corpuscular hemoglobin concentration (MCHC), red blood cell count, or platelet number, and measurements of white blood cell count were inconclusive. Single gavage doses of ≤30 μg/kg 2,3,4,7,8-pentaCDF or ≤15 μg/kg 2,3,7,8-tetraCDF produced no treatment-related hematological changes in Hartley guinea pigs observed for 30 days (Moore et al. 1979). Mild anemia, mild lymphopenia, and marked neutrophilia developed in rhesus monkeys following single ≥500 μg/kg doses of 2,3,7,8-tetraCDF (Moore et al. 1979).

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In intermediate duration studies, C57BL/6Fh mice treated with 300 μg/kg/day 2,3,7,8-tetraCDF by gavage on 22 days in a 30-day period had decreased total leukocytes with no changes in differential count or other hematological indices (Moore et al. 1979). The NOAEL in this study is not known because lower dosages were not evaluated. Other studies with 2,3,7,8-tetraCDF showed normal leukocyte counts (other indices not evaluated) in guinea pigs treated by weekly gavage with ≤l μg/kg for 6 weeks (Luster et al. 1979a, 1979b), and no alterations in blood cell counts in rhesus monkeys treated by diet with 0.21 μg/kg/day for 6 months or 2.1 μg/kg/day for 2 months (McNulty et al. 1981). Although peripheral blood cell counts were normal in these monkeys, histological examinations showed hypocellularity of the bone marrow. Hematological evaluations were performed in 1va:SIV 50 (SD) rats that were fed 2,3,4,7,8-pentaCDF, 1,2,3,4,8-pentaCDF, 1,2,3,7,8-pentaCDF or 1,2,3,6,7,8-hexaCDF for 13 weeks (Pluess et al. 1988a, 1988b; Poiger et al. 1989). A few alterations (e.g., decreased hemoglobin, decreased thrombocyte count, increased platelets, increased white blood cells and/or increased packed cell volume) were observed at dosages of ≥0.1 μg/kg/day 2,3,4,7,8-pentaCDF and 10 μg/kg/day 1,2,3,7,8-pentaCDF or 1,2,3,6,7,8-hexaCDF, but the only consistent finding was 7-9% decreased hemoglobin. Due to the uncertain physiological significance of the small percentage decreases in hemoglobin with no changes in red blood cell count, and the sporadic occurrence of other hematological effects which could be related to general systemic toxicity, none of the changes are considered to be adverse. No treatment-related hematologic alterations occurred in the rats treated with 1,2,3,4,8-pentaCDF (the only non-2,3,7,8-substituted congener tested) at dosages as high as 300 μg/kg/day. Dietary exposure to uncharacterized mixtures of two tetra-, four penta-, and four hexaCDFs for 4 weeks caused hemolytic anemia in blood smears, reduced hemoglobin, hematocrit and MCV, and/or increased MCHC in rats at ≥50 μg/kg/day (Oishi and Hiraga 1978; Oishi et al. 1978).

The above findings indicate that mild anemia is a fairly consistent hematological effect of 2,3,7,8-substituted CDFs in humans and animals. Responses, however, varied among congener, animal species, and dose and duration of exposure.

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

Reduced muscle mass, but no histological alterations in muscle, was observed in Hartley guinea pigs that were administered a single gavage dose of ≥5 μg/kg 2,3,7,8-tetraCDF or ≥3 μg/kg

2,3,4,7,8-pentaCDF (Moore et al. 1979). The reduced muscle mass appears to be a manifestation of a generalized wasting syndrome (see Other Systemic Effects).

No studies were located regarding musculoskeletal effects in animals after intermediate or chronic duration oral exposure to CDFs.

Hepatic Effects. Mild hepatic alterations have been described in Yusho and Yu-Cheng patients (Kuratsune 1989; Rogan 1989). Markedly increased serum triglycerides with unchanged serum cholesterol was an abnormal laboratory finding peculiar to both Yusho and Yu-Cheng exposure (Okumura et al. 1979; Uzawa et al. 1969). The elevated triglycerides generally persisted for several years following exposure and subsequently declined to normal. Yusho patients have shown few abnormalities in serum levels of liver enzymes or in liver function tests (Kuratsune 1989), but elevations in serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) are fairly consistent findings in Yu-Cheng patients (Rogan 1989). Increased urinary excretion of uroporphyrin, but not coproporphyrin or porphobilinogen, is another consistent finding in Yu-Cheng patients, including children born to exposed mothers (Chang et al. 1980; Gladen et al. 1988; Lu et al. 1980).

Ultrastructural changes, particularly alterations in the endoplasmic reticulum, and pleomorphic and enlarged mitochondria appear to be the predominant morphological finding in Yusho patients (Kuratsune 1989). Approximately half of 24 deaths observed in 2,061 Yu-Cheng victims by the end of 1983 were attributed to cirrhosis, unspecified liver diseases with hepatomegaly or hepatoma (Hsu et al. 1985). Diagnoses were made from clinical symptoms and unspecified laboratory examinations. These findings are inconclusive due to unreported background incidences and high prevalences of hepatitis B, cirrhosis, and liver cancer in Taiwan (Rogan et al. 1989).

Hepatic effects in animals following acute duration oral exposure to CDFs were mild to moderate in severity. Microsomal mixed function oxygenase (MFO) enzyme induction is one of the most sensitive hepatic effects of CDFs and is consistent with ultrastructural changes in the endoplasmic reticulum. This effect was not considered adverse if it occurred with no pathologic or other biochemical changes. Assays for activity of the MFO aryl hydrocarbon hydroxylase (AHH) were performed in Sprague-Dawley rats 3 days following a single 40 μg/kg gavage dose of 25 di-, tetra-, penta-, hexa-, hepta-, and octaCDF congeners (Doyle and Fries 1986). Hepatic AHH activity was significantly increased (2.1- to

4.7-fold) by three congeners with chlorine in all four lateral positions (2,3,7,8-tetraCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,4,6,7,8,9-octaCDF), and the 2,7- and 2,8-diCDFs, but other doses and end points were not evaluated. A single gavage dose of 53 μg/kg 2,3,4,7,8-pentaCDF produced hepatic biochemical changes (increased microsomal 7-ethoxyresorufin 0-deethylase [EROD] activity, decreased vitamin A content) in Sprague-Dawley rats, but there was no change in relative liver weight, and histology was not evaluated (Ahlborg et al. 1989). Single gavage doses of ≥100 μg/kg 2,3,4,7,8-pentaCDF were hepatotoxic to Fischer-344 rats as indicated by a spectrum of dose-related effects observed after 35 days, including increased EROD activity and relative liver weight, increased serum cholesterol (nearly doubled in all groups 7 days postexposure), and lipid accumulation in liver with biliary hyperplasia at ≥500 μg/kg (Brewster et al. 1988). Effects including increased SGOT activity and gall bladder and bile duct epithelial hypertrophy, but no other changes in liver histology or relative weight, were observed in rhesus monkeys 60 days after single lethal doses (≥1,000 μg/kg) of 2,3,7,8-tetraCDF (Moore et al. 1979). Studies with Hartley guinea pigs showed no histological alterations in the liver or gall bladder 30 days after single gavage doses as high as 15 μg/kg 2,3,7,8-tetraCDF or 30 μg/kg 2,3,4,7,8-pentaCDF, which were lethal (Moore et al. 1979). Unspecified hepatic histological alterations suggestive of mild liver toxicity were observed in C57BV6Fh mice examined 30 days after a single nonlethal dose of 6,000 μg/kg/day 2,3,7,8-tetraCDF (Moore et al. 1976, 1979).

Intermediate duration studies indicate that 2,3,7,8-substituted CDFs are more hepatotoxic than other congeners. Liver toxicity was assessed in Iva:SIV 50 (SD) rats that were fed 2,3,4,7,8-pentaCDF, 1,2,3,4,8-pentaCDF, 1,2,3,7,8-pentaCDF, or 1,2,3,6,7,8-hexaCDF for 13 weeks (Pluess et al. 1988a, 1988b; Poiger et al. 1989). A spectrum of effects including increased relative liver weight, increased serum alkaline phosphatase, cholesterol and bilirubin, decreased serum triglycerides and SGPT, and/or fatty and necrotic changes, were observed at dosages of ≥0.1 μg/kg/day 2,3,4,7,8-pentaCDF, ≥1 μg/kg/day 1,2,3,6,7,8-hexaCDF and 10 μg/kg 1,2,3,7,8-pentaCDF. No treatment-related hepatic alterations occurred in the rats treated with 1,2,3,4,8-pentaCDF at dosages as high as 300 μg/kg/day. Hepatic effects in rats exposed to an uncharacterized dietary mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks included increased hepatic uroporphyrin concentrations at 250 μg/kg/day and increased liver weight, lipid content, and serum cholesterol at ≥97 μg/kg/day (Oishi and Hiraga 1978; Oishi et al. 1978). Based on the LOAEL for hepatic effects (increased serum bilirubin, decreased serum triglycerides) in rats, an intermediate oral MRL of 0.00003 ug/kg/day was calculated for 2,3,4,7,8-pentaCDF as described in footnote “c” in Table 2-l. Increased height and number of

goblet cells in the bile duct epithelium were the only hepatic histological alterations found in rhesus monkeys that died from dietary ingestion of 2,3,7,8-tetraCDF dosages of 0.21 μg/kg/day for 6 months or 2.1 μg/kg/day for 2 months (one animal per dose examined) (McNulty et al. 1981). These alterations were not accompanied by chemical-related changes in serum levels of liver-associated enzymes. Relative liver weight was increased in C57BL/6Fh mice 30 days following gavage of ≥30 μg/kg/day 2,3,7,8-tetraCDF on 22 days in a 30-day period, but lower dosages were not tested and other hepatic end points were not reported (Moore et al. 1979).

No studies were located regarding hepatic effects in animals after chronic duration oral exposure to CDFs.

The previous studies indicate that the liver is an important target of CDFs. Animal tests performed primarily in rats and monkeys indicate that congeners substituted in the 2,3,7,8 positions are most hepatotoxic. Insufficient studies are available on other species to assess differences in sensitivity to CDFs.

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to CDFs.

Acute duration studies have found mild renal effects in animals exposed to lethal doses of CDFs. Hyperplasia of the epithelium in the renal pelvis, ureter and urinary bladder was observed in Hartley guinea pigs 30 days after single gavage doses of ≥10 μg/kg 2,3,7,8tetraCDF or 2,3,4,7,8-pentaCDF (Moore et al. 1979). It is unclear from this report whether or not this effect also occurred in guinea pigs treated with 5 μg/kg 2,3,7,8-tetraCDF or 3 μg/kg 2,3,4,7,8-pentaCDF, the only nonlethal dose groups in which histology was evaluated. Increased relative kidney weight, decreased absolute kidney weight, and 64% increased blood urea nitrogen (BUN) was found in Fischer-344 rats observed for 35 days following a single gavage dose of ≥500, ≥1,000, and 2,000 μg/kg 2,3,4,7,8-pentaCDF, respectively (Brewster et al. 1988). Reduced body weight contributed to the increased relative kidney weights. There were no histological alterations in the kidneys or bladder in any of the treated rats. Because both organ weight and functional (BUN) changes occurred at 2000 mg/kg, this dose is a LOAEL. No histological alterations were observed in the kidneys of C57B1/6Fh mice 30 days after a single, nonlethal gavage dose of 6,000 μg/kg/day 2,3,7,8-tetraCDF (Moore et al. 1979). Blood urea nitrogen was increased in rhesus monkeys administered a single gavage dose of ≥1,000 μg/kg

2,3,7,8-tetraCDF only during the period that immediately preceded death, but this was not accompanied by altered kidney weight or histology, and only small numbers were evaluated (Moore et al. 1979).

In intermediate duration studies, there were no treatment-related kidney histological alterations in 1va:SIV 50 (SD) rats that ingested ≤10 μg/kg 2,3,4,7,8-pentaCDF, 1,2,3,7,8-pentaCDF or 1,2,3,6,7,8-hexaCDF, or ≤300 μg/kg 1,2,3,4,8-pentaCDF, via diet for 13 weeks (Pluess et al. 1988a, 1988b; Poiger et al. 1989). Kidney histology was not evaluated in Sprague-Dawley rats exposed to ≤960 μg/kg/day of an uncharacterized dietary mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks (Oishi et al. 1978). However, based on unchanged relative kidney weight, no adverse effects were observed. No studies were located regarding renal effects in animals after chronic duration exposure.

In conclusion, mild to moderate renal effects have been observed in guinea pigs, rats, and monkeys exposed to lethal doses of 2,3,7,8-tetraCDF or 2,3,4,7,8-pentaCDF. Information on other congeners and species is not available.

Derma/Ocular Effects. Effects in the skin and eyes, the most obvious manifestations of Yusho and Yu-Cheng exposure, have been observed in the majority of cases and have been evaluated in numerous studies (Hsu et al. 1993; Kuratsune 1989; Lu and Wu 1985; Rogan 1989). Characteristic skin changes included marked enlargement, elevation and keratotic plugging of follicular orifices, comedo formation, acneform eruptions, hyperpigmentation, hyperkeratosis, and deformed nails. The acne most commonly developed in the face and other parts of the head, axillae, trunk and external genitalia, with follicular plugging occurring in the axillae, groin, glenoid regions such as elbow and knee flexures, trunk, thigh, and outer aspect of the forearm. Dark-colored pigmentation frequently occurred in the gingival and buccal mucosa, lips, and nails and improved only gradually in most patients. Most patients showed eye discharge and other severe ocular effects during the acute phase of the Yusho and Yu-Cheng syndrome (Fu 1984; Kuratsune 1989; Lu and Wu 1985; Rogan 1989). These effects include meibomian gland changes (enlargement, inflammation, hypersecretion of cheese-like material) and dark-colored pigmentation of the conjunctivae and eyelids. Improvement of the ocular changes was gradual and occurred with improvement of dermal effects.

Limited information is available on dermal or ocular effects of CDFs in animals following acute oral exposure. Rhesus monkeys that were treated with single, nonlethal (500 μg/kg) or lethal

(≥1000 μg/kg) doses of 2,3,7,8-tetraCDF and observed for 60 days developed progressive and dose-related skin lesions (Moore et al. 1979). These included dry leathery skin, facial edema, loss of eyelashes and fingernails, exudate with occlusion and squamous metaplasia of eyelid (meibomian) and ear canal (ceruminous) glands, epidermal hyperkeratosis, and dilation of sebaceous gland ducts, and, at 1,500 ug/kg, follicular hyperkeratosis. No skin or eye histological alterations were observed in Hartley guinea pigs 30 days after single gavage doses of ≤15 μg/kg 2,3,7,8-tetraCDF or ≤30 μg/kg 2,3,4,7,8-pentaCDF, or in C57BU6Fh mice similarly treated with 6,000 μg/kg 2,3,7,8-tetraCDF (Moore et al. 1979).

Dermal lesions also developed in rhesus monkeys treated with 2,3,7,8-tetraCDF in intermediate-duration studies (McNulty et al. 1981). Dietary dosages of 0.21 μg/kg/day for ≤6 months caused periorbital edema, meibomian gland enlargement, partial atrophy of sebaceous glands and hyperkeratotic nail beds. Similar exposure to a higher dosage of 2.1 μg/kg/day caused more severe skin changes, including eyelid reddening and thickening and partial facial hair loss after 1 month, and body hair and nail loss and absent sebaceous glands. Surviving monkeys were completely recovered 2-3 months after either exposure. Chloracne-like lesions developed on the ear of Sprague-Dawley rats exposed to 960 μg/kg/day dietary dosages of an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks (Oishi et al. 1978). No studies were located regarding dermal effects in animals after chronic duration oral exposure to CDFs.

As discussed above, effects in the skin and eye are the most obvious manifestations of CDF toxicity on humans and animals. The studies in animals, although limited by number of congeners and species tested, indicate that 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF are active and that monkeys are more sensitive than rodents.

Other Systemic Effects. One of the major effects of CDFs in animals is a wasting syndrome that has been observed in acute and intermediate duration studies (no chronic studies have been performed). The syndrome is characterized by progressive decreased weight gain, with immediate moderate to severe body weight loss generally occurring at near-lethal doses. Single gavage doses have caused wasting effects in guinea pigs at ≥3 μg/kg 2,3,4,7,8-pentaCDF or ≥5 μg/kg 2,3,4,7,8-pentaCDF or 2,3,7,8-tetraCDF (Moore et al. 1976, 1979), rats at ≥500 μg/kg 2,3,4,7,8-pentaCDF (Brewster et al. 1988) and monkeys at ≥500 μg/kg 2,3,7,8-tetraCDF (Moore et al. 1979). In intermediate duration studies, body weight gain was decreased in Iva:SIV 50 (SD) rats fed

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≥1 μg/kg/day dosages of 2,3,4,7,8-pentaCDF or a 10 μg/kg/day dosage of 1,2,3,7,8-pentaCDF or 1,2,3,6,7&hexaCDF for 13 weeks, with a higher lethal dosage of 2,3,4,7,8-pentaCDF (10 μg/kg/day) causing approximately 50% weight loss (Pluess et al. 1988a, 1988b; Poiger et al. 1989). Similar treatment with ≤300 μg/kg/day 1,2,3,4,8-pentaCDF did not affect rat body weight. Body weight gain was decreased in Sprague-Dawley rats exposed to ≥97 μg/kg/day dietary dosages of an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks (Oishi et al. 1978). Studies with a CDF mixture similar to that in Yusho oil showed decreased body weight gain in Sprague-Dawley rats exposed to 44 μg/kg/day for 22 days and body weight loss in cynomolgus monkeys exposed to 8 μg/kg/day for 80-113 days (Kunita et al. 1984). Rhesus monkeys administered 0.21 μg/kg/day 2,3,7,8-tetraCDF in diet for 6 months had normal growth except for a brief period of rapid weight loss prior to death (McNulty et al. 1981). Other gavage studies of 2,3,7,8-tetraCDF showed no treatment-related effects on body weight in Hartley guinea pigs administered weekly doses of ≤1 μg/kg/day for 6 weeks (Luster et al. 1979a, 1979b) or in C57BL/6Fh(J67) mice treated with ≤300 μg/kg/day on 22 days in a 30-day period (Moore et al. 1979). In conclusion, animals studies have demonstrated that 2,3,7,8-substituted tetra-, penta-, and hexaCDF congeners induce wasting in all species and duration categories tested.

Endocrinological evaluations of Yu-Cheng patients found a tendency for increased urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids (Nagai et al. 1971). Effects on reproductive endocrinology in Yu-Cheng patients have also been reported (see Section 2.2.2.5)

Limited information is available on effects of CDFs on endocrine organs in animals. Adrenal hemorrhage, but no histological changes in the thyroid or pancreas, were found in Hartley guinea pigs that received single, lethal, gavage doses of ≥10 μg/kg/day 2,3,7,8-tetraCDF or 2,3,4,7,8-pentaCDF (Moore et al. 1979). Adrenal histology was normal in Iva:SIV 50 (SD) rats administered dietary dosages of ≤10 μg/kg/day 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, or 1,2,3,6,7,8-hexaCDF, or ≤300 μg/kg/day 1,2,3,4,8-pentaCDF, for 13 weeks (Pluess et al. 1988a, 1988b; Poiger et al. 1989). These dosages were sublethal except for 10 μg/kg/day 2,3,4,7,8-pentaCDF. No consistent effects on serum hydrocortisone levels occurred in Hartley guinea pigs treated by gavage with weekly ≤1 μg/kg/day doses of 2,3,7,8-tetraCDF for 6 weeks (Luster et al. 1979a, 1979b). Effects on the thymus are discussed in Section 2.2.2.3 (Immunological Effects).

2.2.2.3 Immunological Effects

Clinical observations strongly suggest that Yusho and Yu-Cheng patients experienced frequent or more severe skin and respiratory infections and lowered resistance to illness (Kuratsune 1989; Rogan 1989). Various changes in immune status have been reported in Yusho and Yu-Cheng patients, including decreased serum IgA and IgM levels and lymphocyte subpopulations, diminished phagocyte complement and IgG receptors, and diminished delayed-type skin hypersensitive response (Chang et al. 1981, 1982a, 1982b; Lu and Wu 1985; Nakanishi et al. 1985; Shigematsu et al. 1971). Immune status was normal in children 7-9 years old who had *in utero* Yu-Cheng exposure (Lan et al. 1990).

Decreased thymus weight and thymic atrophy, characterized by lymphoid cell loss, involutions and/or lack of corticomedullary differentiation, have been consistently observed in animals exposed to CDFs. Thymus weight decreases were often pronounced, particularly at lethal doses where reductions as high as 80-90% have been observed. Decreased thymus weight and histologic atrophic changes in thymus (e.g., lymphoid depletion) occurred following single gavage doses of ≥100 μg/kg/day 2,3,4,7,8-pentaCDF in Fischer-344 rats (Brewster et al. 1988), ≥3 μg/kg/day 2,3,4,7,8-pentaCDF and ≥5 μg/kg/day 2,3,7,8-tetraCDF in Hartley guinea pigs (Moore et al. 1979), and ≥1,000 μg/kg/day 2,3,7,8-tetraCDF in rhesus monkeys (Moore et al. 1979). Based on the LOAEL for thymic histopathology in guinea pigs, an acute oral MRL of 0.001 μg/kg/day was calculated for 2,3,4,7,8-pentaCDF as described in footnote "b" in Table 2-l. Thymus weight was also decreased in Sprague-Dawley rats fed ≈44 μg/kg/day of a CDF mixture similar to that in Yusho oil for 10 days (Kunita et al. 1984). No thymic or splenic histological alterations were observed in C57b1/6Fh mice 30 days after a single gavage dose of 6,000 μg/kg 2,3,7,8-tetraCDF (Moore et al. 1979). In intermediate duration studies with Iva:SIV 50 (SD) rats, dose-related changes progressing from decreased thymus weight to thymic atrophy resulted from 13-week dietary treatment with ≥0.1 μg/kg/day 2,3,4,7,8-pentaCDF, ≥1 μg/kg/day 1,2,3,6,7,8-hexaCDF or ≥10 μg/kg/day 1,2,3,7,8-pentaCDF, but not with ≤300 mg/kg/day 1,2,3,4,8-pentaCDF (Pluess et al. 1988a, 1988b; Poiger et al. 1989). Dietary exposure to an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks caused decreased thymus weight at ≥97 μg/kg/day in Sprague-Dawley rats (Oishi et al. 1978). Reduced thymus weight with mild atrophic changes developed in Hartley guinea pigs treated with weekly gavage doses of ≥0.5 μg/kg/day 2,3,7,8-tetraCDF for 6 weeks (Luster et al. 1979a, 1979b). Thymus weights were decreased in ICR/JCL mice treated with four weekly 100 μg/kg gavage doses of a mixture containing 88% pentaCDFs and 12% tetraCDFs (congeners not identified)

(Oishi and Hiraga 1980), and in C57BL/6fh(J67) mice treated with 300 μg/kg/day 2,3,7,8-tetraCDF by gavage on 22 days in a 30-day period (lower doses not evaluated) (Moore et al. 1979). Thymic atrophic changes, including small lobules without cortices and marked involution, were found in rhesus monkeys that were fed diets containing 2,3,7,8-tetraCDF dosages of 0.21 μg/kg/day for 6 months or 2.1 μg/kg/day for 2 months (McNulty et al. 1981). Effects on the thymus also occurred in offspring of rats exposed during gestation (see Section 2.2.2.6).

Pathological changes in immune system tissues other than thymus were also observed in some of the above studies. These included hypocellularity of bone marrow and lymphoid elements in spleen and Peyer's patches of guinea pigs given single doses of ≥3 μg/kg/day 2,3,4,7,8-pentaCDF or ≥5 μg/kg/day 2,3,7,8-tetraCDF (Moore et al. 1979), and increased extramedullary hematopoiesis in splenic red pulp and occasional atrophic changes in lymph nodes in rats treated with ≥1 μg/kg/day 2,3,4,7,8-pentaCDF for 13 weeks (Pluess et al. 1988a, 1988b; Poiger et al. 1989). There were no treatment-related histological changes in lymph nodes or spleen in rats similarly treated with ≤10 μg/kg/day 1,2,3,7,8-pentaCDF or 1,2,3,6,7,8-hexaCDF or ≤300 mg/kg/day 1,2,3,4,8-pentaCDF. Six weekly doses of ≤1 μg/kg/day 2,3,7,8-tetraCDF caused no changes in spleen weight or histology in guinea pigs (Luster et al. 1979a, 1979b). Spleen weight in mice was unaffected by four weekly ≤100-μg/kg doses of a pentaCDFs/tetraCDFs mixture (Oishi and Hiraga 1980). The ED_{50} for decreased splenic response to intraperitoneally injected sheep red blood cells was 208 μg/kg in mice given a single oral dose of 1,2,3,4,6,7,8-heptaCDF (Kerkvliet et al. 1985).

Limited information on effects of CDFs on immunocompetence is available from above studies. Guinea pigs treated with six weekly doses of 0.5 μg/kg/day 2,3,7,8-tetraCDF had significantly decreased macrophage inhibition index but no significant effect on another cell-mediated immunity indicator, delayed hypersensitivity index (Luster et al. 1979a, 1979b). There were no treatment-related effects on humoral immune function as indicated by serum protein levels (albumin and alpha, beta, and gamma globulins) and IgG antibody responses. Proliferation of lymphocytes following *in vitro* stimulation with the T-lymphocyte mitogen phytohemagglutinin and the B-lymphocyte mitogen lipopolysaccharide were significantly decreased at ≥0.5 μg/kg/day, but the T-lymphocyte mitogen concanavalin A had no effect. Studies of mortality from injected *Escherichia coli* lipopolysaccharide endotoxin in mice treated with four weekly 100 μg/kg doses of a pentaCDFs/tetraCDFs mixture were inconclusive (Oishi and Hiraga 1980). In conclusion, the limited number of studies available suggest that CDFs have the potential to impair immunocompetence and that thymic effects are part of the

spectrum of adverse effects on the immune system. Immunologic effects have been observed in all animal species tested, but mice appear to be less sensitive than other rodents and monkeys. Based on the animal data, the most potent congeners are those substituted in the 2,3,7,8 positions, particularly, 2,3,4,7,8-pentaCDF. The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and acute- and intermediate-duration categories are recorded in Table 2-l and plotted in Figure 2- 1.

2.2.2.4 Neurological Effects

Various neurological symptoms, including numbness, weakness and neuralgia of limbs, hypesthesia and headaches, are common in Yusho and Yu-Cheng victims (Chia and Chu 1984, 1985; Kuratsune 1989; Rogan 1989). Conduction velocities were reduced in sensory nerves (radial and/or sural) in 9 of 23 Yusho patients examined soon after poisoning (Kuroiwa et al. 1969). Sensory fibers may have been preferentially affected as conduction velocities in motor nerves (ulnar and tibial) were reduced in only two cases and motor functions were normal. Follow-up studies were not performed on the Yusho patients, but disappearance of related symptoms and signs indicated that the effects on nerve conduction did not persist. Reduced sensory and motor nerve conduction velocities also occurred in Yu-Cheng patients (Chen et al. 1985a; Chia and Chu 1984, 1985). Evaluation of 110 patients within 1 year of Yu-Cheng exposure showed abnormally slow sensory nerve (median and ulnar) and motor nerve (tibia1 and peroneal) conduction velocities in ≈44% and 22% of the patients, respectively (Chen et al. 1985a). All of the subjects had developed eye and skin manifestations of toxicity, but there were no significant correlations between nerve conduction values and blood levels of PCBs, CDFs or PCQs. Electroencephalographic examination of Yu-Cheng patients did not show any abnormalities potentially indicative of central nervous system damage (Chia and Chu 1984, 1985). Neurobehavioral deficits have been observed in children born to mothers with Yu-Cheng exposure (see Section 2.2.2.6).

Limited information is available on possible neurological effects of CDFs in animals. Signs of toxicity in Fischer-344 rats given single, lethal doses of 2,3,4,7,8-pentaCDF included piloerection, splayed and hunched posture, and hypoactivity at ≥1,000 μg/kg, and tremors and lacrimation in one animal at 2,000 μg/kg (Brewster et al. 1988). Single gavage doses of ≤30 μg/kg 2,3,4,7,8-pentaCDF or ≤15 μg/kg 2,3,7,8-tetraCDF to guinea pigs or ≤6,000 μg/kg 2,3,7,8-tetraCDF to mice produced no histological alterations in the brain during the following 30 days (Moore et al. 1979). Dietary exposure to an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks

caused grossly observable cerebral edema and flabby brain appearance in Sprague-Dawley rats at ≥97 μg/kg/day, but slight fluid accumulation also occurred in the thorax and abdomen (Oishi et al. 1978). The effects observed in the above studies are not necessarily indicative of a direct effect on the central nervous system and could be secondary to other changes (e.g., wasting syndrome, stress) occurring in intoxicated or dying animals. Because more sensitive neurological tests were not performed, insufficient information is available for evaluating the neurotoxic potential of CDF congeners in animals, and effect levels for neurological effects are not recorded in Table 2-l or plotted in Figure 2- 1.

2.2.2.5 Reproductive Effects

Irregular menstrual cycles and abnormal basal body temperature patterns were observed in ≈60% and 85% of female Yusho patients, respectively (Kusuda 1971). These alterations were accompanied by decreased urinary excretion of estrogens, pregnanediol, and pregnanetriol, and possibly suggest corpus luteum insufficiency and retarded follicular maturation. Fertility, fecundity and rates of spontaneous abortion have not been studied in Yusho and Yu-Cheng patients (Kuratsune 1989; Rogan 1989).

Limited information is available on possible reproductive effects of CDFs in animals. Hypocellularity of the seminiferous tubules was observed in Hartley guinea pigs given single gavage doses of ≥3 μg/kg/day 2,3,4,7,8-pentaCDF or ≥5 μg/kg/day 2,3,7,8-tetraCDF (Moore et al. 1979). There were no testicular histological changes in rats treated with a single gavage dose of ≤2,000 μg/kg 2,3,4,7,8-pentaCDF (Brewster et al. 1988). Histology of the testis, ovary, and uterus was normal in Iva:SIV 50 (SD) rats administered dietary dosages of ≤10 μg/kg/day 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF or 1,2,3,6,7,8-hexaCDF, or ≤300 μg/kg/day 1,2,3,4,8-pentaCDF, for 13 weeks (Pluess et al. 1988a, 1988b; Poiger et al. 1989). Dietary exposure to an uncharacterized mixture of two tetra-, four penta-, and four hexaCDFs for 4 weeks caused increased testes weight at ≥97 μg/kg/day and decreased seminal vesicle and ventral prostate weights and decreased testicular testosterone concentration at 960 μg/kg/day in Sprague-Dawley rats (Oishi et al. 1978). The apparent increase in testes weight may be due to concurrent depression of total body weight. The animal data suggest that the testis is a target of CDFs, although information on reproductive function is not available and insufficient data preclude assessing species and congener differences. The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and acute- and intermediate-duration categories are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.6 Developmental Effects

Skin lesions are commonly observed in children born to mothers with Yusho or Yu-Cheng exposure. The dermal changes are consistent with those observed in exposed adults (see Section 2.2.2.2) and include hyperpigmentation of the skin, nails and gingivae, deformed nails, conjunctivitis, and acne (Funatsu et al. 1971; Gladen et al. 1990; Hsu et al. 1985, 1993; Rogan et al. 1988; Taki et al. 1969; Yamaguchi et al. 1971; Yoshimura 1974). These effects generally diminished as the babies grew older. Eight of 39 hyperpigmented children born to Yu-Cheng-intoxicated mothers died perinatally due to pneumonia, bronchitis, and prematurity (Hsu et al. 1985). Decreased birth weight is another commonly reported effect of Yusho and Yu-Cheng exposure (Funatsu et al. 1971; Lan et al. 1987; Rogan 1989; Taki et al. 1969; Yamaguchi et al. 1971). A health survey of most (117) living children known to have been *in utero* during or after Yu-Cheng exposure found that mean birth weight was decreased ≈15% (Gladen et al. 1990; Rogan et al. 1988). Neurobehavioral assessment based on parental reports showed that 49% of these children were delayed (older) in achieving developmental milestones compared to 22% of unexposed children, but this was not clearly corroborated by neurological examiners (Rogan et al. 1988; Yu et al. 1991). Cognitive testing (Bayley mental and psychomotor developmental indices, Stanford-Binet test, Wechsler Intelligence Scale for Children) showed significantly lower overall age-adjusted developmental scores in the exposed children. Delays were seen at all ages and were greater in children who were smaller in size, had neonatal signs of intoxication and/or had a history of nail deformities. Results of follow-up testing (Stanford-Binet test and Wechsler Intelligence Scale) when the children were 4-7 years old indicate that effects on cognitive development persisted for several years following exposure (Chen et al. 1992). Urinary excretion of total porphyrins was mildly increased in children of Yu-Cheng mothers (Gladen et al. 1988). Immune status was normal in Yu-Cheng children 7-9 years old (Lan et al. 1990).

It is well established that CDFs are teratogenic in rats and mice, inducing dose-related kidney hydronephrosis and/or cleft palate at incidences as high as 100%. Hydronephrosis and cleft palate were induced in C57BL/6N mice by gavage doses as low as 10 and 50 μg/kg/day 2,3,7,8-tetraCDF, respectively (Weber et al. 1984, 1985); 5 and 30 μg/kg/day 2,3,4,7,8-pentaCDF, respectively (Birnbaum et al. 1987a, 1987b); 30 and 100 μg/kg/day 1,2,3,7,8-pentaCDF, respectively (Bimbaum et al. 1987a); and 100 and 300 μg/kg/day 1,2,3,4,7,8-hexaCDF, respectively (Bimbaum et al. 1987a, 1987b). These data are consistent in indicating that hydronephrosis is a more sensitive developmental effect than cleft palate in mice. However, none of the teratology studies in mice examined fetal sites

other than kidney or palate (e.g., nonrenal soft tissues or skeleton), or tested strains other than C57BL/6N. ED_{50} values for hydronephrosis and cleft palate were estimated as 7 and 36 μg/kg/day, respectively, for 2,3,4,7,8-pentaCDF, 54 and 133 μg/kg/day, respectively, for 1,2,3,7,8pentaCDF, and 81 and 342 μg/kg/day, respectively, for 1,2,3,4,7,8hexaCDF (Birnbaum et al. 1987a). Toxic effects generally were not observed in mouse dams or fetuses but occurred in some studies at doses equal to or higher than the lowest doses causing teratogenic effects. Fetal edema is a characteristic fetotoxic effect that has been observed visibly or suggested by increased fetal weight. One exception is a report of increased fetal mortality and hydronephrosis in mice occurring at the same doses (≥250 μg/kg/day) of 2,3,7,8-tetraCDF (Weber et al. 1984), but this was not confirmed in another mouse study by the same investigators using similar doses of this congener (Weber et al. 1985). Administration of 80 μg/kg/day of 2,3,4,7,8-pentaCDF caused hemorrhagic lesions in the placenta of C57BL/6N mice (Khera 1992).

Decreased fetal weight, increased fetal mortality, and cleft palate occurred in fetuses of Fischer-344 rats treated with ≥30, ≥100, and 300 μg/kg/day 2,3,4,7,8-pentaCDF, respectively (Couture et al. 1989). No hydronephrosis or other kidney or nonrenal soft tissue anomalies were observed, although fetal relative thymus and lung weights were decreased at 300 μg/kg/day. Missing or delayed thoracic vertebrae and sternebrae were observed at all dose levels (≥30 μg/kg/day) including controls, and cranial ossification was delayed at 300 μg/kg/day. These changes likely represent delayed development, but assessment is complicated by unreported quantitative data for the effects on the vertebrae and sternebrae. There was some evidence of maternal toxicity (e.g., decreased thymus weight) at all tested doses. The fetal mortality data suggest that rats are more sensitive than mice to fetotoxic effects of CDFs.

Mean relative thymus weight was decreased ≈6%, 14%, and 30% in l-week-old offspring of Wistar SPF rats gavaged with 0.5, 2, or 30 μg/kg/day 2,3,4,7,8-pentaCDF, respectively, on gestation day 16 (Madsen and Larsen 1989). This was accompanied by increased hepatic microsomal enzyme activity, but no other end points were evaluated. Interpretation of this study is complicated by lack of tabulated data and reported statistical analysis in the report, but ATSDR evaluation using the Mann-Whitney test shows that the decreases in thymus weight at ≥2 μg/kg/day are statistically significant. The discrepancy in LOAELs for reduced offspring thymus weight in this and the other rat study (Couture et al. 1989) is likely due to the additional exposure received through nursing, although different days of treatment and interstrain differences in sensitivity could also be factors. As discussed in

Section 2.2.2.3 (Immunological Effects), the thymus is also one of the most sensitive targets of CDFs in adult animals. In conclusion, 2,3,7,8 substituted tetra-, penta-, and hexaCDFs induced hydronephrosis, cleft palate, thymic effects, and/or other developmental changes in animals. Rats appear to be more sensitive than mice, although only two studies were performed with mice and other species were not tested, and 2,3,4,7,8-pentaCDF and 2,3,7,8-tetraCDF were the most potent tested congeners. The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and acute-duration category are recorded in Table 2- 1 and plotted in Figure 2- 1,

2.2.2.7 Genotoxic Effects

The levels of sister chromatid exchanges and chromosome aberrations were examined in peripheral lymphocytes of 12 Yu-Cheng nonsmoker women 5 years after they had consumed rice oil contaminated with CDFs and PCBs (Lundgren et al. 1988). In the presence of α-naphthoflavone, the frequency of sister chromatid exchanges was significantly increased in exposed subjects. This finding was explained by postulating that subjects exposed to PCBs and CDFs have increased concentrations of P-450 monoxygenase in lymphocytes which could result in increased formation or retention of metabolites of α-naphthoflavone causing sister chromatid exchanges. The increase in sister chromatid exchanges was correlated with serum PCB congeners, but not with serum levels of CDFs. Chromosome aberration frequencies were similar in control and exposed populations. No studies were located regarding genotoxic effects in animals after oral exposure to CDFs. Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

A retrospective mortality study of 887 male and 874 female patients that were observed for an average of 11 years following official registration as Yusho victims found no significant increase in male deaths (79 observed, 66.13 expected) or female deaths (41 observed, 48.90 expected) from all causes (Kuratsune et al. 1987). Mortality for cancer at all sites, however, was significantly increased in males (33 observed, 15.51 expected, standardized mortality ratio [SMR]=2.13) based on Japanese national rates. This is attributable to significantly increased mortality from liver cancer (9 observed, 1.61 expected, SMR=5.89) and cancer of the lung, trachea, and bronchus (8 observed, 2.45 expected, SMR=3.26). The increased mortality from liver cancer remained statistically significant when based on local death rates (SMR=2.53) and when early liver cancer cases (those occurring <9 years after

poisoning) were excluded (SMR=3.85). However, because the geographic distribution of liver cancer deaths was unexpectedly markedly uneven (there was no significant increase in one of two prefectures), the cancer cannot be conclusively associated with Yusho exposure.

Approximately half of 24 deaths observed in 2,061 Yu-Cheng victims by the end of 1983 were attributed to hepatoma, cirrhosis, or unspecified liver diseases with hepatomegaly (Hsu et al. 1985). Diagnoses were made from clinical symptoms and unspecified laboratory examinations. These findings are inconclusive due to unreported incidences and comparison values and high prevalences of hepatitis B, cirrhosis, and liver cancer in Taiwan (Rogan et al. 1989).

No studies were located regarding cancer in animals after oral exposure to CDFs.

2.2.3 Dermal Exposure

2.2.3.1 Death

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

Mortality occurred in hairless mice that were treated with 1,2,3,4,7,8-hexaCDF in acetone in dermal initiation-promotion studies (Hebert et al. 1990). As detailed in Section 2.2.3.8, a single application of acetone or *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) initiator to intact uncovered skin was followed by promotion with twice weekly applications of 1,2,3,4,7,8-hexaCDF or 2,3,4,7,8-pentaCDF for 20 weeks. Mice pretreated with acetone or MNNG followed by 3.3 or 33.3 µg/kg/day hexaCDF, respectively, experienced 35% mortality compared to 0% in controls. No significant effects on survival were observed in the mice pretreated with acetone or MNNG and promoted with ≤3.3 µg/kg/day 2,3,4,7,8-pentaCDF. The LOAEL value for death in the acetone pretreated mice is recorded in Table 2-2, but the LOAEL for MNNG pretreatment is not included because of the likelihood of interactions that could increase the toxicity of CDFs.

2.2.3.2 Systemic Effects

NOAEL and LOAEL values for systemic effects of dermal exposure to CDFs are available from an intermediate duration mouse initiation-promotion study that used a single application of MNNG or

TABLE 2-2. Levels of Significant Exposure to CDFs - Dermal

Species	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
INTERMEDIATE EXPOSURE							
Death							
Mouse	20 wk 2 d//wk 1x/d				3.3 (35% mortality)	Hebert et al. 1990	hexa
Systemic							
Mouse	20 wk 2 d//wk 1x/d	Gastro		3.3 (mucous cell hyperplasia of glandular stomach)		Hebert et al. 1990	hexa
		Hepatic		3.3 (increased liver weight and hypertrophy)			
		Other		33.3 (8% body weight loss)			
Mouse	20 wk 2 d//wk 1x/d	Gastro	3.3			Hebert et al. 1990	penta
		Hepatic		3.3 (increased liver weight and hypertrophy)			
		Other		3.3 (12% decreased body weight gain)			
Immunological							
Mouse	20 wk 2 d//wk 1x/d				3.3 (thymic and spleen atrophy)	Hebert et al. 1990	hexa
Mouse	20 wk 2 d//wk 1x/d				3.3 (thymic and spleen atrophy)	Hebert et al. 1990	penta
Cancer							
Mouse	20 wk 2d/wk 1x/d				8.3 (CEL; skin proliferative lesions following initiation)	Hebert et al. 1990	hexa

TABLE 2-2. Levels of Significant Exposure to CDFs - Dermal (*continued*)

Species	Exposure duration/ frequency	System	NOAEL (µg/kg/day)	LOAEL (effect) Less serious (µg/kg/day)	LOAEL (effect) Serious (µg/kg/day)	Reference	Congener
Mouse	20 wk 2d/wk 1x/d				33.3 (CEL; skin papillomas following initiation)	Poland et al. 1982	tetra
Mouse	20 wk 2d/wk 1x/d				0.08 (CEL; Skin proliferative lesions following initiation)	Hebert et al. 1990	penta

CDFs = chlorinated dibenzofurans; CEL = cancer effect level; d = day(s); Gastro = gastrointestinal; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s); x = times

hexa = 1,2,3,4,7,8-hexachlorodibenzofuran
penta = 2,3,4,7,8-pentachlorodibenzofuran
tetra = 2,3,7,8-tetrachlorodibenzofuran

acetone as the initiator (Hebert et al. 1990). Effect levels in the acetone pretreated mice are recorded in Table 2-2 but values for MNNG pretreatment are not included for noncancer end points due to concern for possible interactive effects on CDF toxicity.

No studies were located regarding respiratory, cardiovascular, hematological, musculoskeletal, or renal effects in humans or animals after dermal exposure to CDFs.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to CDFs.

Mucous cell hyperplasia developed in the glandular stomach of hairless mice treated with 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF on intact uncovered skin in dermal initiation-promotion studies (Hebert et al. 1990). As detailed in Section 2.2.3.8, initiation with a single application of acetone or MNNG was followed by promotion with twice weekly applications of 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF for 20 weeks. The incidence of stomach hyperplasia was significantly increased in the mice pretreated with acetone and followed by 3.3 μg/kg/day hexaCDF, but not 3.3 μg/kg/day pentaCDF. Stomach hyperplasia also developed in the mice initiated with MNNG and promoted with 3.3 yg/kg/day pentaCDF or ≥8.3 μg/kg/day hexaCDF. No stomach hyperplasia was observed in control groups. It is not known if CDF ingestion from grooming contributed to exposure.

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

Increased relative liver weight and histological hypertrophy were observed in hairless mice treated on intact uncovered skin in dermal initiation-promotion studies (Hebert et al. 1990). As detailed in Section 2.2.3.8, initiation with a single application of acetone or MNNG was followed by promotion with twice weekly applications of 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF for 20 weeks. The hepatic changes were observed in 100% of the mice pretreated with acetone and followed by 3.3 μg/kg/day pentaCDF or 3.3 μg/kg/day hexaCDF, as well as mice initiated with MNNG and promoted with ≥0.08 μg/kg/day pentaCDF or ≥8.3 μg/kg/day hexaCDF. Livers were normal in control groups.

Derma/Ocular Effects. No studies were located regarding dermal or ocular effects in humans after dermal exposure to CDFs.

Dermal initiation-promotion studies were performed using hairless mice that were treated with 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF on intact uncovered skin (Hebert et al. 1990). As detailed in Section 2.2.3.8, initiation with a single application of acetone or MNNG was followed by promotion with twice weekly applications of 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF for 20 weeks. No information was reported on nonproliferative dermal effects in mice pretreated with acetone and followed by either pentaCDF or hexaCDF, so dermal toxicity of CDFs alone (i.e., not initiated by MNNG) cannot be clearly evaluated. Dermal changes of possible relevance to CDFs alone occurred in mice initiated with MNNG and promoted with pentaCDF (0.08-3.3 μg/kg/day) or hexaCDF (8.3-33.3 μg/kg/day). Dermal toxicity was evaluated by a mean score based on number of mice within a group with no, mild, moderate, or severe gross changes. Gross effects ranged from coarse and thickened appearance of skin to desquamation. Histological alterations included epidermal hyperplasia, squamous metaplasia of sebaceous glands, inflammation of dermis and atrophy, or loss of hair follicles and sebaceous glands.

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

Effects on body weight gain occurred in hairless mice that were treated with 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF on intact uncovered skin in dermal initiation-promotion studies (Hebert et al. 1990). As detailed in Section 2.2.3.8, initiation with a single application of acetone or MNNG was followed by promotion with twice weekly applications of 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF for 20 weeks. Weight gain decreased (12.5%) significantly in the mice pretreated with acetone followed by 3.3 μg/kg/day pentaCDF. Those pretreated with acetone followed by 33.3 μg/kg/day hexaCDF lost weight. The mice initiated with MNNG showed decreased weight gain with promotion by 3.3 μg/kg/day pentaCDF or 8.3 or 16.7 μg/kg/day hexaCDF, and weight loss with promotion by 33.3 μg/kg/day hexaCDF.

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans after dermal exposure to CDFs.

Decreased thymus and spleen weights with atrophy occurred in hairless mice that were treated with 2,3,4,78-pentaCDF or 1,2,3,4,7,8-hexaCDF on intact uncovered skin in dermal initiation-promotion studies (Hebert et al. 1990). As detailed in Section 2.2.3.8, initiation with a single application of acetone or MNNG was followed by promotion with twice weekly applications of 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF for 20 weeks. Both relative thymus and spleen weights were significantly reduced in mice pretreated with acetone and followed by 3.3 μg/kg/day pentaCDF or 3.3 μg/kg/day hexaCDF. In mice initiated with MNNG, thymus weight was decreased by promotion with ≥1.7 μg/kg/day pentaCDF or ≥8.3 μg/kg/day hexaCDF, and spleen weight was decreased by promotion with 3.3 μg/kg/day pentaCDF or ≥16.7 μg/kg/day hexaCDF. Prominent lymphoid atrophy in both thymus and spleen at "higher" dosages of pentaCDF and hexaCDF was reported but not detailed. The LOAEL values for immunological effects for each congener in the acetone pretreated mice are recorded in Table 2-2, but values for MNNG pretreatment are not included due to concern for interactive effects on CDF toxicity.

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

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to CDFs.

Initiation-promotion studies were performed in which a single 5 μmol dose of MNNG initiator was applied to intact uncovered skin of hairless (hr/hr) mice followed by promotion with twice weekly dermal doses of 0.08-3.3 μg/kg 2,3,4,7,8-pentaCDF or 8.3-33.3 μg/kg 1,2,3,4,7,8-hexaCDF for 20 weeks (Hebert et al. 1990). Acetone was used as the vehicle for the MNNG and CDFs. The penta- and hexaCDFs were also tested using acetone as the control initiator at a dose of 3.3 μg/kg/day.

Mice initiated with acetone or MNNG and promoted with acetone were used as controls. There were no significant increases in proliferative lesions of the skin in the mice pretreated with acetone and followed by pentaCDF or hexaCDF, although there was an observation period following treatment. However, proliferative skin lesions developed in 77.8-94.4% and 47.1-89.5% of the mice initiated with MNNG and promoted with ≥0.08 μg/kg pentaCDF or ≥8.3 μg/kg hexaCDF, respectively, compared to 10.5% in the control groups. Most of the lesions were hyperproliferative nodules and squamous cell papillomas. In a similarly designed tumor promotion study using 2,3,7,8-tetraCDF, hairless mice were initiated with a single 5 μmol dermal dose of MNNG in acetone followed by twice weekly dermal applications of ≈33.3 μg tetraCDF/kg in acetone for 20 weeks (Poland et al. 1982). Skin papillomas developed in 100% of the mice, compared to control group incidences of 5% in mice initiated with acetone and promoted with tetraCDF and 0% in mice initiated with MNNG and promoted with acetone. These findings indicate that tetraCDF, pentaCDF, and hexaCDF had skin tumor promotion activity. The cancer effect levels (CELs) for each congener are recorded in Table 2-2.

2.3 TOXICOKINETICS

Data regarding toxicokinetics of CDFs in humans are limited to information derived from cases of accidental ingestion and/or exposure by the inhalation and dermal routes. Humans can absorb CDFs by the inhalation, oral, and dermal routes of exposure. CDFs, when administered orally, are well absorbed by experimental animals, but are absorbed less efficiently when administered by the dermal route. Data regarding absorption in animals after inhalation exposure were not available. Absorption rates depend on the chlorine substitution pattern and vehicle used. Tissue distribution of CDFs is similar in humans and animals. Due to their lipophilic nature, CDFs tend to accumulate in lipid-rich tissues. High amounts of CDFs are usually found in the liver, adipose, skin, and muscle. Accumulation in tissues is strongly dependent on the chlorine substitution pattern, which in turn, determines the rate of metabolism. CDFs are metabolized predominantly by cytochrome P-450 to polar metabolites that undergo glucuronidation. Substitutions in positions 4 and 6 impair biotransformation, so that CDFs with these positions substituted, in addition to lateral substitutions (2,3,7,8), are preferentially retained or excreted unchanged. This is true for humans and animals. Data from animal studies show that fecal excretion of metabolites is the main route of excretion of CDFs, regardless of the route of exposure. The exact mechanism of CDF toxicity is not known. It

has been suggested, however, that the mechanism is related to the enhancement of gene expression triggered by initial binding to a cytosolic Ah receptor.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Quantitative data regarding inhalation absorption of CDFs in humans after controlled inhalation exposure to CDFs were not located. However, absorption of CDFs can be inferred from the fact that CDFs have been detected in tissues and blood of subjects after accidental or occupational exposure to airborne CDFs (Schecter and Ryan 1989; Schecter et al. 1991). These subjects were exposed to soot or dust containing CDFs during clean-up operations following a PCB transformer fire or associated with municipal solid waste incineration. The relative contribution of the dermal route cannot be determined.

No studies were located regarding absorption of CDFs in animals after inhalation exposure to CDFs.

2.3.1.2 Oral Exposure

Indirect evidence of oral absorption of CDFs in humans can be derived from the fact that CDFs were detected in blood and in numerous organs and tissues of subjects who ingested rice oil contaminated with CDFs in the Yusho and Yu-Cheng incidents (Chen et al. 1985b; Masuda et al. 1985).

A recent study examined absorption of CDFs from maternal milk in a 3-month-old infant (Jodicke et al. 1992). Analysis of the milk and the infant's stools showed that some highly chlorinated CDF congeners were more concentrated in the stools than in the milk suggesting that these congeners were less well absorbed or more resistant to enterohepatic circulation than those with lower chlorine content. Results from a balance sheet analysis showed that over 95% of the total CDFs in the milk were removed from the intestinal tract of the infant (Jodicke et al. 1992).

In male Hartley guinea pigs, >90% of a single oral dose of 6 μg of ^{14}C-2,3,7,8-tetraCDF/kg in Emulphor/ethanol/water was absorbed over a 3-day period (Decad et al. 1981a). In female Sprague-Dawley rats administered single doses of three different CDFs mixed in food pellets at 3.5-6.3 μg/kg

body weight, 80% of the 2,3,4,7,8-pentaCDF dose was retained in the liver in 24 hours, compared to 34% for 1,2,3,7,8-pentaCDF and 43% for 1,2,3,6,7,8-hexaCDF (Van den Berg et al. 1989). In this study, liver retention was used as an indirect measure of absorption. When similar doses of the CDFs were administered in peanut oil, the amount of retained 1,2,3,7,8-pentaCDF doubled, the amount of retained 2,3,4,7,8-pentaCDF was unchanged, and the amount of retained 1,2,3,6,7,8-hexaCDF increased to 58%. Excretion data showed that male Fischer-344 rats administered single oral doses of 34, 169, or 338 μg ^{14}C-2,3,4,7,8-pentaCDF/kg in corn oil absorbed >70% of the dose over a 3-day period, regardless of the dose; absorption rate, over the dose range tested, was not dose-related (Brewster and Bimbaum 1987). High absorption (≈90%) was also reported for 2,3,7,8-tetraCDF in male Fischer-344 rats administered a single gavage dose of the CDF in Emulphor/ethanol (Birnbaum et al. 1980).

The limited data regarding oral absorption of CDFs in animals suggest that, in general, these compounds are well absorbed and that absorption efficiency depends on the vehicle and the chlorine substitution pattern. However, clear relationships between structure and absorption cannot be established from the available data, since, for example, peanut oil appeared to facilitate absorption of 1,2,3,7,8-pentaCDF and 1,2,3,6,7,8-hexaCDF, but not of 2,3,4,7,8-pentaCDF (Van den Berg et al. 1989).

2.3.1.3 Dermal Exposure

Quantitative data regarding dermal absorption of CDFs in humans after controlled dermal exposure to CDFs were not located. However, absorption of CDFs can be inferred from the fact that CDFs have been detected in the tissue and blood of subjects after accidental exposure (Schecter and Ryan 1989). These subjects were exposed to soot or dust containing CDFs derived from a PCB transformer fire. Exposure occurred during clean-up operations that followed the fire. In these cases, however, the relative contribution of the inhalation route cannot be determined.

Limited information is available regarding dermal absorption of CDFs in animals. Dermal absorption of 1,2,3,7,8-pentaCDF and 2,3,4,7,8-pentaCDF was studied in male Fischer-344 rats, (Brewster et al. 1989). In these animals, 25% and 34% of a dose of 34 μg/kg of ^{3}H-1,2,3,7,8-pentaCDF and ^{14}C-2,3,4,7,8 pentaCDF in acetone, respectively, was absorbed from the clipped back skin over a 3-day period. In the same time period, 49% of a dose of ^{14}C-2,3,7,8-tetraCDF was absorbed. For these three

CDFs, the percentage of the administered dose absorbed decreased as the applied dose increased. For doses near 300 μg/kg of the three CDFs tested, ≈80% of the radioactivity associated with the application site could be removed by swabbing with an acetone-soaked cotton, indicating that the remaining radioactivity had not penetrated through the dermis. In male Fischer-344 rats, the percentage of the administered dose (34 μg/kg) of ^{14}C-2,3,4,7,8-pentaCDF absorbed through the skin over a 3-day period decreased with age (Banks et al. 1990). The greatest decrease was observed between 10- and 36-week-old rats (22% of the administered dose compared to 15% for the adult rats). When absorption rate was expressed as a function of the applied surface area, in order to eliminate the body weight variable, the mass of 2,3,4,7,8-pentaCDF absorbed by the l0-week-old rats was greater than that observed in 36- and 120-week-old animals.

The available information indicates that over a 3-day period, the rates for dermal absorption of tetraand pentaCDFs in animals are half or less than half those observed for oral absorption.

2.3.2 Distribution

Data from autopsy reports from two adult individuals, not known to have been exposed to high concentrations of CDFs, revealed the presence of CDFs in four tissues: abdominal and subcutaneous fat, liver, muscle, and kidney (Ryan et al. 1985a). The CDFs detected were penta-, hexa-, and heptaCDFs. On a whole weight basis, adipose tissue had the greatest amount of CDFs, followed by liver, muscle, and kidney. The most prevalent CDFs were 1,2,3,4,7,8-hexaCDF and 1,2,3,6,7,8-hexaCDF. When the results were expressed on a lipid basis, the concentration of total CDFs did not vary greatly among tissues. A subsequent report by the same group of investigators showed that CDFs were also present in human adrenal and bone marrow (Schecter et al. 1989a). No CDFs could be detected in brain, pancreas, thymus, heart, and testis of a &month-old infant or a 22-year-old adult (Ryan et al. 1986).

Other distribution studies on CDFs in tissues of infants have been performed. In these cases, exposure to CDFs may have occurred in utero and through breast milk. CDFs were reported in the liver and adipose tissue of a breast-fed infant born to a mother with Yu-Cheng (Masuda et al. 1985). Beck et al. (1990) detected CDFs in the brain, adipose tissue, thymus, spleen, and liver of three infants who died of sudden infant death before reaching 1 year of age. Maternal exposures were not reported. Of the three infants, only one had been breast fed for a significant period of time (≈6 months). The

congeners identified in most tissues of the three infants were 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,6,7,8-hexaCDF, and 1,2,3,4,6,7,8-heptaCDF. The most prevalent were 2,3,4,7,8-pentaCDF and 1,2,3,6,7,8-hexaCDF. On a fat weight basis, the brain and adipose tissue had relatively low levels of CDFs, whereas the liver had the highest levels, in particular in the infant who had nursed. The congeneric composition did not differ among tissues or across infants. Unequivocal placental transfer of CDFs was demonstrated by detecting CDFs in the liver of stillborn infants (Schecter et al. 1990a).

The mechanism by which CDFs cross biological membranes is not known; however, it can be assumed that due to their lipophilic nature, penetration of membranes can be easily accomplished.

2.3.2.1 Inhalation Exposure

Data regarding distribution of CDFs in humans following controlled inhalation exposure were not located. However, as indicated in Section 2.3.2.3, CDFs were detected in samples of adipose tissue in a subject involved in clean-up operations that followed an electrical transformer fire (Schecter and Ryan 1989). The relative contribution of the dermal exposure is not known.
No studies were located regarding distribution of CDFs in animals after inhalation exposure to CDFs.

2.3.2.2 Oral Exposure

Data regarding distribution of CDFs in humans are derived mainly from the Yusho and Yu-Cheng incidents, in which individuals consumed rice oil contaminated predominantly with PCBs and CDFs. The concentration of total CDFs in adipose tissue and liver of deceased Yusho patients ranged from 3 to 25 ppb (Masuda et al. 1985). No CDFs were detected in unexposed individuals in that study; however, subsequent studies using more sensitive analytical methods detected CDFs in tissues of unexposed Japanese and Chinese individuals (Ryan et al. 1987a) (see Section 5.5). In general, the congeners identified in the tissue and blood of Yusho patients consisted of congeners with unsubstituted adjacent carbon atoms, the most prevalent of which was 2,3,4,7,%pentaCDF. The least prevalent was 2,3,7,8-tetraCDF. Similar results were obtained by analyzing adipose and liver tissues of an infant born to a Yu-Cheng mother (indicating *in utero* transfer or through nursing, or both) and in blood of Yu-Cheng patients (Kashimoto et al. 1985; Masuda et al. 1985). Since ≈40 different CDF

congeners were identified in the contaminated rice oil, these results suggest preferential metabolism and retention for certain CDF congeners (see Section 2.3.3). Analyses of tissues of a Yu-Cheng patient who died 2 years after poisoning revealed that the liver had the highest concentration of CDFs (≈35 ppb); the concentration in other tissues was one or more than one order of magnitude lower than in the liver (Chen et al. 1985b). The major CDF congeners retained in the liver were 1,2,4,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, and 1,2,3,4,7,8-hexaCDF. The congeneric profile for tissues other than the liver was essentially similar to that of the liver.

Several studies have examined the distribution of CDFs in animals after oral intake. Three days after administration of single gavage doses of 31 or 306 μg ^{14}C-2,3,7-tetraCDF/kg in Emulphor/ethanol to male Fischer-344 rats, the CDF-derived radioactivity was accumulated in liver (3-5%), fat (4-9%), and skin (1%) (Birnbaum et al. 1980). No significant differences were observed between the two dose levels. Muscle and blood accounted for <1% of the total dose.

Male Fischer-344 rats received a single oral dose of ^{14}C-2,3,4,7,8-pentaCDF at 34-338 μg/kg, and 3 days after dosing, CDF-derived radioactivity was most concentrated in the liver (>50%), followed by adipose (6%), skin (0.9%), and muscle (0.5%) (Brewster and Birnbaum 1987). When expressed as percentage of the dose per gram of tissue, the liver had 5.9% followed by adipose with 0.3%, and adrenal with 0.15%. Regardless of how the results were expressed, tissue distribution was not dose-related, and all other tissues and organs had only traces of radioactivity.

The distribution of CDFs in pregnant C57BW6N mice and in the embryos was examined after oral administration of 800 μg ^{14}C-2,3,7,8-tetraCDF/kg in corn oil to the dams on gestation day 11 (Weber and Birnbaum 1985). Approximately 30% and 0.41% of the dose-derived radioactivity per gram of tissue was found in the dams' livers and blood, respectively (only maternal liver and blood were analyzed), on gestation day 12; these percentages declined by half in both tissues on subsequent days. Elimination half-life from the liver was 1.5 days. Less than 0.01% of the dose was detected in whole embryos at day 12, and no radioactivity could be detected at later times. A dose of 1,000 μg 2,3,7,8-tetraCDF/kg causes 100% cleft palate in mice (Weber and Birnbaum 1985).

Experiments conducted in male Hartley guinea pigs administered 6 μg of labeled 2,3,7,8-tetraCDF/kg by gavage in Emulphor/ethanol/water showed that most of the CDF-derived radioactivity (46%) accumulated in fat 3 days after dosing (Decad et al. 1981a). Liver, muscle, and skin accounted for

≈16% each. After six or seven weekly doses of 2,3,7,8-tetraCDF at 1 µg/kg the distribution of radioactivity in the tissues of guinea pigs was similar to that observed after a single oral dose (Decad et al. 1981a).

Distribution studies suggest that, due to their lipophilic nature, CDFs tend to accumulate in lipid-rich tissues such as skin and adipose. Since tissue levels were determined 3 days after dosing in rats and guinea pigs, early redistribution processes between, for example, liver and other tissues are difficult to ascertain. The two studies in rats, one with 2,3,7,8tetraCDF (Birnbaum et al. 1980) and the other with 2,3,4,7,8-pentaCDF (Brewster and Birnbaum 1987), clearly indicate that a relationship exists between substitution pattern and liver retention; >50% of the 2,3,4,7,8-pentaCDF was retained, compared with only 3-5% for the 2,3,7,8 congener. This is because substitution in position 4 appears to delay metabolic transformation (Burka et al. 1990). This was clearly demonstrated in rats, in which 1,2,3,7&pentaCDF had a liver retention half-life of 3.3 days, whereas that for 2,3,4,7,8-pentaCDF was 108 days (Van den Berg et al. 1989). Similar findings were reported in mice in which the elimination half-times from the liver for 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF were 1.5 days (Weber and Birnbaum 1985) and 65 days (de Jongh et al. 1992), respectively.

2.3.2.3 Dermal Exposure

Data regarding distribution of CDFs in humans following dermal exposure were not located. However, CDFs were detected in samples of adipose tissue in a subject involved in clean-up operations that followed an electrical transformer fire (Schecter and Ryan 1989). The relative contribution of the inhalation route of exposure is not known. Four determinations were made over a period of 3 years starting 2 years after exposure. The most prevalent congeners found (consecutive determinations, ppt on a lipid basis) were 2,3,4,7,8-pentaCDF (84, 52, 46, 54), 1,2,3,4,7,8-hexaCDF (143, 101, 65, 63), 1,2,3,6,7,8-hexaCDF (97, 85, 79, 50), and 1,2,3,4,6,7,8-heptaCDF (55, 29, 39, 32). When expressed on a lipid basis, the concentration of the CDF congeners in serum and adipose tissue was similar.

Tissue distribution of CDFs was studied in male Fischer-rats 3 days after receiving single applications of 31-340 µg/kg of labeled 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, or 2,3,4,7,8-pentaCDF in acetone in a clipped area of the back (Brewster et al. 1989). For example, with the lowest dose, the liver had the most CDF-derived radioactivity per tissue (5.4% for 2,3,7,8-tetraCDF, 4.1% for 1,2,3,7,8-pentaCDF,

14.9% for 2,3,4,7,8pentaCDF), followed by adipose tissue, skin, and muscle. All other tissues (other than liver, adipose, skin, and muscle) had <0.01% of the dose. The relative amounts of radioactivity per tissue decreased as the dose increased, reflecting decreased absorption. Expressed as a percentage of total body burden, 2,3,4,7,8-pentaCDF-derived radioactivity (percentage of absorbed dose) detected in the liver and adipose tissue was 72% and 6.7%, respectively. The concentration of radioactivity per gram of tissue was the greatest in the liver with 2,3,4,7,8-pentaCDF > 2,3,7,8-tetraCDF ≥ 1,2,3,7,8-pentaCDF. Again, as pointed out for oral exposure, these results indicate that liver retention is significant and congener specific, with significantly higher amounts of the pentaCDF substituted in position 4 retained.

No significant age-related changes in the distribution of 2,3,4,7,8-pentaCDF in rats were observed (Banks et al. 1990). For the most part, changes in tissue distribution reflected age-related changes in the total mass of specific tissues and organs.

2.3.2.4 Other Routes of Exposure

The tissue distribution of CDFs after parenteral dosing has been studied in several animal species. The results for these studies show that, in general, the distribution of CDFs in tissues is similar to that observed after oral or dermal administration of CDFs.

In rhesus monkeys administered a single dose of 30.7 μg ^{14}C-2,3,7,8-tetraCDF/kg intravenously the CDF was rapidly cleared from the blood (Birnbaum et al. 1981). A two component exponential decay from blood was observed, with half-lives of 1.5 minutes and 1 hour, respectively. Terminal components of the removal of 2,3,7,8-tetraCDF from the blood were not determined in the study. After 21 days, <10% of the CDF-derived radioactivity remained in the body. When the concentration of CDF was expressed per gram of tissue, the concentrations in liver and fat were 4 times that observed in skin and 12 times that observed in muscle and blood. Of the radioactivity extracted from liver and adipose tissue at day 21 and from blood just after dosing, ~90% appeared to be parent compound. However, 67% of the label remaining in blood at day 21 seemed to correspond to metabolites.

The distribution of radiolabeled 2,3,7,8-tetraCDF has also been studied in rats following intravenous injection, After a single dose of 30.6 μg/kg to male Fischer-344 rats, the blood, liver, fat, skin, and

muscle accounted for >90% of the unexcreted dose of CDF at various times after dosing (Birnbaum et al. 1980). Nearly all the radioactivity detected in tissues was unchanged CDF. Loss of radioactivity from tissues could be described by exponential curves with one or more components. Half-lives for the early components ranged from 0.02 days for blood and muscle to 0.45 days for skin. Late components had half-lives ranging from 0.72 days for muscle to 11.l days for skin. Clearance from fat showed a single component with a half-life of 3.7 days. In other tissues, such as adrenals, kidney, thymus, heart, and lungs, 90% of the radioactivity was cleared within 24 hours; in contrast, the specific activity in the liver decreased only 50% in the same time period.

As with rats and monkeys, intravenous injection of ^{14}C-2,3,7,8-tetraCDF in guinea pigs (6 μg/kg) resulted in preferential accumulation of radioactivity in liver, fat, muscle, and skin (Decad et al. 1981a). Chromatographic analysis of these tissues suggested the presence of only parent compound. Three hours after dosing, a loss of radioactivity from the liver could be accounted for by an increase in adipose and skin. After 1 day, mobilization of fat stores resulted in redistribution of radioactivity into the liver. Accumulation of radioactivity in other tissues was minimal over a 9-day period.

Results in mice were similar to those obtained in other animal species. CDF-derived radioactivity was concentrated in the liver, adipose tissue, skin, and muscle of C57BL/6J and DBA/2J male mice injected with a single intravenous dose of 30.6 μg ^{14}C-2,3,7,8-tetraCDF/kg (Decad et al. 1981b). These tissues accounted for >75% of the injected dose. At all times over a l0-day period (except at day l0), the livers of C57BL/6J mice had more radioactivity than livers of DBA/2J mice (the opposite was observed for fat tissue and muscle), but the half-life elimination of the CDF-derived radioactivity from this organ was I.8 days in both strains. Elimination half-lives from adipose tissue were 6 times longer in DBA/2J mice than in the C57BW6J strain, reflecting the higher fat tissue content in the former strain. Greater than 95% of the radioactivity detected in tissues represented unmetabolized CDF.

2.3.3 Metabolism

No data were located regarding metabolism of CDFs in humans. However, some information can be derived from Yusho and Yu-Cheng patients. These subjects ingested contaminated rice oil in which ≈40 different CDF congeners were identified. As indicated in Section 2.3.2.2, analysis of hepatic adipose tissues of some patients revealed the presence of highly chlorinated congeners and congeners

that lacked adjacent unsubstituted carbon atoms (Chen et al. 1985b; Masuda et al. 1985). This indicates that the presence of unsubstituted adjacent carbon atoms favors metabolism, which is consistent with data for other chlorinated aromatic hydrocarbons. Highly chlorinated congeners have slower metabolic rates, possibly due to steric hindrance.

The metabolic disposition of CDFs in animals has not been extensively studied. However, some generalizations can be made based on the available data. It is generally accepted that biotransformation of CDFs occurs primarily in the liver (Birnbaum 1985; Van den Berg 1989). The major metabolic reactions include hydroxylations with or without dechlorination or migration of substituents from the site of hydroxylation to the adjacent carbon, and oxygen bridge cleavage, followed by glucuronidation. Cytochrome P-450 isoenzymes appear to catalyze the metabolic reactions (Van den Berg 1989).

The major possible metabolic products (specific compounds were not identified) of several CDFs found in rat bile after oral and intravenous dosing of CDFs have been described (Poiger and Pluess 1989). Female Sprague-Dawley derived rats were administered a single oral dose of several tetra- and pentachlorinated CDFs in corn oil. In addition, 1,2,3,6,7,8-hexaCDF and 1,2,3,4,7,8-heptaCDF were injected intravenously. The doses ranged between 0.4 and 3.7 mg/kg. Samples of bile were analyzed for 3-7 days starting 2 hours after dosing. The tetra-substituted CDFs 1,3,7,8-, 2,3,7,8-, and 2,3,6,8- exhibited a fairly high rate of metabolic conversion (no quantitative data reported), and each gave rise to tri- and tetra- hydroxylated and dihydroxylated derivatives. No ring-opened compounds were detected, suggesting that substitution of *ortho* atoms to the oxygen is not important for cleavage of the ether bond in tetraCDFs. A recent study by Burka et al. (1990) identified glucuronide and sulfate conjugates of 4-hydroxy-2,3,7,8-tetraCDF and 3-hydroxy-2,7,8-triCDF as the major biliary metabolites in rats dosed intravenously with 2,3,7,8-tetraCDF.

Among the pentaCDFs, the rate of transformation of 1,2,3,4,8-, 1,2,3,7,8-, and 2,3,4,7,8-pentaCDF was high, moderate, and low, respectively (Poiger and Pluess 1989). The predominant metabolite (out of seven compounds found) of 1,2,3,7,8-pentaCDF was a hydroxy-pentaCDF. According to investigators, formation of 6,7-dihydroxy-pentaCDF may also have occurred. Tetrachlorinated compounds were also identified. The major metabolite (out of 12 compounds found) of 1,2,3,7,8-pentaCDF was a dihydroxy-pentaCDF; other derivatives included monohydroxy-tetra- and pentaCDFs and a trichloro-dihydroxyCDF. Metabolism of 2,3,4,7,8-pentaCDF led to two major compounds (out of 10

compounds found), a methoxy-pentaCDF, and a dimethoxy-pentachlorobiphenyl, the latter formed by ether cleavage. A sulfur containing metabolite was also present. Unmetabolized pentaCDFs were also excreted in the bile. Only a small amount of a hydroxy-pentaCDF was identified from 1,2,3,6,7,8-hexaCDF, whereas no metabolites were detected from 1,2,3,4,6,7-heptaCDF.

No metabolites were detected in urine, feces, liver, and adipose tissue of male Wistar rats given a single gavage dose of 250 mg/kg octaCDF in peanut oil (Veerkamp et al. 1981).

The main conclusions regarding metabolic transformation of CDFs are that chlorine substituents in positions four or six, in addition to the lateral positions, inhibit metabolism more than chlorines in positions one and nine, and that metabolic rate strongly decreases as the number of chlorine atoms increases.

2.3.4 Excretion

Since CDFs have been found in human milk samples from a number of countries (Schecter 1991; Van den Berg et al. 1986), breast feeding is a potential source of excretion (and exposure for the infant) for these compounds. CDFs were reported in the liver and adipose tissue of a breast-fed infant born to a mother with Yu-Cheng (Masuda et al. 1985).

2.3.4.1 Inhalation Exposure

Data regarding excretion of CDFs in humans after the inhalation/dermal route are discussed in Section 2.3.4.3.

No studies were located regarding excretion of CDFs in animals after inhalation exposure to CDFs.

2.3.4.2 Oral Exposure

Limited information is available regarding excretion of CDFs or metabolites in humans after oral exposure to CDFs. Data from Yu-Cheng patients showed that many CDF congeners, which were constituents of the contaminated rice oil, were preferentially excreted, since they could not be detected in tissues of these individuals months or years after exposure (Masuda et al. 1985). For two of the

congeners that were preferentially retained, 2,3,4,7-pentaCDF and 1,2,3,4,7,8-hexaCDF, elimination half-lives of ≈2-2.5 years have been estimated (Ryan et al. 1993).

Analysis of the stools from Yusho patients 22 years after the contamination episode showed a high concentration of penta and hexaCDFs relative to control subjects (Iida et al. 1992). For example, 2,3,4,7,8-pentaCDF was on the average 20 times more concentrated in the stools of Yusho patients than in controls.

Results from a recent study in which CDFs were monitored in an infant's feces after breast feeding suggested that the feces may be the preferred route of elimination of highly chlorinated CDF congeners (Jodicke et al. 1992). No further information regarding excretion could be inferred from this study.

Male Fischer-344 rats excreted ≈70% of ^{14}C-2,3,7,8-tetraCDF-derived radioactivity in the feces over a 3-day period (Birnbaum et al. 1980). The CDF was administered by gavage in Emulphor/ethanol at 31 or 306 ug/kg. In the same time period, urinary excretion accounted for ≈1.5% of the administered dose.

Similar results have been reported in mice (Weber and Birnbaum 1985). Pregnant C57BL/6N mice administered a single dose of 800 μg ^{14}C-2,3,7,8-tetraCDF/kg by gavage in corn oil on day 11 of gestation excreted 80% of the administered dose in the feces over a 3-day period. Urinary excretion accounted for 5.4% of the dose. The estimated whole body half-life was ≈2.6 days.

In contrast to rats and mice, male Hartley guinea pigs excreted 11% of ^{14}C-tetraCDF-derived radioactivity in the feces over the same time period after receiving a gavage dose of 6 μg/kg in Emulphor/ethanol/water (Decad et al. 1981a). Urinary excretion accounted for 3.3% of the administered dose. The fact that 2,3,7,8-tetraCDF is retained for a longer time by guinea pigs, compared to rats and mice, is consistent with the greater toxicity exhibited by this congener in guinea pigs (see Section 2.2).

Studies with other congeners reveal that the extent of excretion is not only species-dependent, but also congener-specific. For example, when single doses between 34 and 338 μg ^{14}C-2,3,4,7,8-pentaCDF/kg were administered to male Fischer-344 rats, ≈30% of the CDF-derived radioactivity was excreted in

the feces over a 3-day period, regardless of the dose (Brewster and Birnbaum 1987). No radioactivity was detected in expired air, and urinary excretion accounted for <0.01% of the dose per day. Analysis of fecal samples 1 day after dosing suggested that >50% of the CDF-derived radioactivity was parent compound; however, 2 days later this fell to 20%. These results, when compared with those obtained with the tetra-substituted congener in rats (Birnbaum et al. 1980), suggest that by adding a chlorine substitute to position four in the CDF ring, excretion rate is decreased by half. As indicated in Section 2.3.3, this is related to the metabolic handling of the two congeners.

In summary, data in rats, guinea pigs, and mice suggest that excretion rates for CDFs after oral dosing are species-dependent and congener-specific. In addition, the relative percentage of derivatives excreted in the feces and urine appears to be species-specific, but the fecal route of elimination is predominant.

2.3.4.3 Dermal Exposure

Data regarding excretion of CDFs in humans exposed by the dermal route were not available. However, relevant information regarding elimination of CDF congeners from adipose tissue can be provided from data on an individual exposed to soot from a transformer accident (Schecter and Ryan 1989). Intake of CDFs resulted most likely from a combination of inhalation and dermal exposure, but the relative contribution of each of these routes is not known. Half-lives for elimination were calculated from four determinations made over a period of 3.5 years, starting 2 years after the accident occurred. Assuming first-order kinetics and subtracting background values, half-lives of 0.3 years, between 1.3 and 1.7 years, and 0.5 years were calculated for 1,2,3,4,6,7,8-heptaCDF, 1,2,3,4,7,8-hexaCDF, and 2,3,4,7,8-pentaCDF, respectively. A more recent publication by the same group of investigators (Schecter et al. 1990b) extended the observations on the same subject over a 6-year period and reported blood-adipose combined half-lives of 4.5, 4.0, 4.9, and 6.8 years for 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,6,7,8-hexaCDF, and 1,2,3,4,6,7,8-heptaCDF, respectively. These values were calculated without accounting for background levels.

Excretion of CDFs was studied in male Fischer-344 rats after receiving single applications of 3-340 μg/kg of labeled 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, or 2,3,4,7,8-pentaCDF in acetone in a clipped area of the back (Brewster et al. 1989). Elimination of CDF-derived radioactivity occurred almost exclusively through the feces. For each congener, the relative amount of radioactivity detected

in the excreta decreased as the dose increased. At the lowest dose tested, fecal excretion accounted for 27% of radioactivity for 2,3,7,8-tetraCDF, 8% for 1,2,3,7,8-pentaCDF, and 0.7% for 2,3,4,7,8-pentaCDF. Within 3 days of dosing, 56%, 32%, and 2% of the respective body burden of 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, and 2,3,4,7,8-pentaCDF had been excreted. Two or more polar metabolites were detected in the feces of rats administered 31 μg 2,3,7,8-tetraCDF/kg and 34 ug 1,2,3,7,8-pentaCDF/kg. Approximately 90% of the 2,3,4,7,8-pentaCDF-derived fecal radioactivity appeared to be parent compound. Excretion parameters for 2,3,4,7,8-pentaCDF-derived radioactivity did not change as a function of age in male Fischer-rats (Banks et al. 1990).

These results are consistent with the view that, due to inhibited metabolism, CDF congeners with substitution in position 4 (2,3,4,7,8-penta) are excreted slower than those with unsubstituted position 4 (2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF). This may be also related to the fact that only parent compound was found in the feces of rats given 2,3,4,7,8-pentaCDF, whereas polar metabolites could be detected in feces of those given 2,3,7,8-tetraCDF and 1,2,3,7,8-pentaCDF.

2.3.4.4 Other Routes of Exposure

In male rhesus monkeys that received a single intravenous injection of 30.7 μg ^{14}C-2,3,7,8-tetraCDF/kg, <10% of the CDF-derived radioactivity remained in the body 21 days after the injection (Birnbaum et al. 1981). The excretion of CDF-derived radioactivity followed a single exponential decay curve both in urine and feces. Half-lives for excretion in urine and feces were 6.2 and 10.3 days, respectively. Over the 21-day period, 8% and 43% of the total dose was excreted in the urine and feces, respectively. Whole body half-life was ≈8 days. Analysis of urine samples revealed at least two polar metabolites and no parent compound. Similarly, feces and bile contained almost exclusively CDF metabolites.

The major route of excretion of ^{14}C-2,3,7,8-CDF in rats treated with a single intravenous dose of the chemical was via the feces (Bimbaum et al. 1980). Five days after dosing, ≈80% of the administered radioactivity had been eliminated through the feces, whereas the majority of the urinary excretion (≈5% of the dose) occurred within the first day. Experiments in rats with cannulated bile ducts showed that enterohepatic circulation does not play a role in the distribution of 2,3,7,8-CDF-derived radioactivity. Half-lives for excretion in urine and feces were 0.3 and 1.8 days, respectively. No parent compound was detected in urine during the 6-day observation period, in bile 3 hours after

dosing, and in feces 2 days after the injection. These results indicate that >99% of the CDF-derived radioactivity excreted from the body consisted of several metabolites and no parent CDF.

In C57BL/6J and DBA/2J male mice, the major route of excretion of ^{14}C-2,3,7,8-tetraCDF-derived radioactivity after a single intravenous dose of 30.6 μg/kg was also the feces (Decad et al. 1981b). Over a l0-day period, >80% of the administered dose in C57BL/6J mice and >55% in DBA/2J mice was excreted in the feces as polar metabolites. Urinary excretion accounted for <20% of the dose in each strain of mice. The nature of the chemicals excreted in the urine shifted from mixed composition (parent compound and metabolites) at early time points to almost all metabolites at day 5. Whole body half-lives were estimated at 2 and 4 days for the C57BW6J and DBA/2J strains, respectively.

In contrast to rats, monkeys, and mice, guinea pigs administered a single intravenous dose of ^{14}C-2,3,7,8-tetraCDF (6 μg/kg) excreted similar amounts of CDF-derived radioactivity in urine and feces, 6.6% of the administered dose in 7 days (Decad et al. 1981a). No CDF-derived radioactivity was detected in bile collected for 4 hours after the injection. In feces, >90% of the radioactivity corresponded to parent compound, whereas one or more polar metabolites were detected in the urine. The estimated whole body half-life for 2,3,7,8-tetraCDF in guinea pigs was ≈20 days.

Several important conclusions can be drawn from studies in which CDFs were administered parenterally. In rats and monkeys given the same congener, fecal excretion is the predominant route of elimination. Whole body half-life is species-dependent, and this appears to be related to toxic potency in different species. This also appears to be valid when comparing toxic potency of different congeners within a species, such that in rats, the more toxic 2,3,4,7,8-pentaCDF has a whole body half-life of 64 days (Brewster and Birnbaum 1987), compared with 8 days for 2,3,7,8-tetraCDF. It should be also pointed out that for congeners with the same number of chlorine substitutions, for example 1,2,3,7,8-pentaCDF (half-life of 7.5 days) and 2,3,4,7,8-pentaCDF (half-life of 64 days), the whole body elimination half-life is determined by the chlorination pattern (due to biotransformation preferences) (Brewster and Birnbaum 1987, 1988).

2.3.5 Mechanism of Action

The mechanism by which CDFs enter the blood stream from the lungs or skin is not known, but it has been suggested that in the gastrointestinal tract, ingested CDFs are incorporated into chylomicra

particles that enter the blood stream (Patterson et al. 1989a). In the blood stream, CDFs are bound to different, very low density lipoproteins, low-density lipoproteins, high-density lipoproteins, and also to protein, most likely prealbumin. In human blood, it has been shown that as the degree of chlorination of the CDF congener increases (from four chlorines up) the percentage of CDF associated with the protein fraction increases, suggesting that higher chlorinated CDFs do not partition according to the lipid content of the fraction (Patterson et al. 1989a). This could indicate the presence of specific interactions between the CDF congeners and the carrier proteins or other proteins.

The mechanism of toxicity for CDFs is not completely understood, but has been extensively studied (Bandiera et al. 1984b; Goldstein and Safe 1989; Mason et al. 1985; Poland and Knutson 1982; Safe 1986, 1990a, 1990b; Skeene et al. 1989). Many CDFs, CDDs, 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 three main lines of information (i.e., structure-receptor binding relationships, structure-induction relationships, and structure-toxicity relationships) (Goldstein and Safe 1989; Safe 1990b, 1991). Most of the studies providing this information investigated compounds other than CDFs, particularly 2,3,7,8-TCDD and other CDDs, and used parenteral routes of exposure and/or *in vitro* test systems. It is beyond the scope of this profile to discuss these studies in detail. The concept of a common mechanism explains why all of these compounds, including CDFs, elicit the same responses and differ only in their relative potency.

Many of the CDFs and related compounds bind to a cellular receptor (Ah receptor), which regulates the synthesis of a variety of proteins. This receptor was identified in the cytosol of mouse liver cells (Poland et al. 1976) and, subsequently, in extrahepatic tissues of laboratory animals, mammalian cell cultures, and human organs and cell cultures. The structure-binding relationships for a series of CDFs were estimated *in vitro* using rat hepatic cytosol preparations (Bandiera et al. 1984b; Mason et al. 1985). Not all CDF congeners showed the same affinity for the Ah receptor; affinity was found to be determined by the chlorine substitution pattern. Those congeners that are isostereomers of 2,3,7,8-TCDD bind with the highest affinity. Tetra- to hexaCDFs that are fully substituted in the lateral two, three, seven, and eight positions are the most active congeners. Affinity constants for CDFs span over a four orders of magnitude range, with 2,3,4,7,8-pentaCDF having the highest affinity (EC_{50}= $1.5x10^{-8}$ M, compared to $1.0x10^{-8}$ for 2,3,7,8-TCDD). All CDFs tested exhibited saturable binding with the Ah receptor and cooperativity was not a factor in these binding interactions (Farrell et al.

1987). The stereospecific nature of the binding strongly suggested the existence of a biological receptor as a mediator in the responses caused by CDFs.

CDFs, as well as the other related halogenated aromatic hydrocarbons, induce a variety of microsomal enzyme activities (cytochrome P-450IAl-dependent monooxygenases) primarily in the liver. The most widely studied of these responses are induction of hepatic AHH and EROD both in mammalian cell cultures and in laboratory rodents (Bandiera et al. 1984b; Brewster et al. 1988; De Vito et al. 1993; Goldstein and Safe 1989; Goldstein et al. 1978; Holcomb et al. 1988; Kawano and Hiraga 1978; Mason et al. 1985; Nebert et al. 1975; Safe 1990b; Safe et al. 1986). Results from a study in male Wistar rats in which the inductive potency of 13 CDF congeners was tested following intraperitoneal dosing showed that only those congeners substituted in positions 2,3,7, and 8 (dioxin-like) exhibited typical 3-methylcholanthrene (MC)-type induction (Yoshihara et al. 1981). Those congeners having two or less chlorine substitutions in the lateral positions did not induce EROD activity. Results from a similar study showed that the structure-activity relationships for liver enzyme inductive potency of a series of CDFs were comparable to those reported for the structure-binding relationships (Mason et al. 1985). Furthermore, a linear correlation was observed between AHH induction in vitro and *in vivo* providing further support to a common receptor-mediated mechanism of action for CDFs.

Structure-toxicity relationships for several CDFs have been studied in immature male Wistar rats *in vivo* and in rat cell cultures *in vitro* (Bandiera et al. 1984b; Holcomb et al. 1988; Mason et al. 1985; Safe et al. 1986). Determination of ED_{50} values for hepatic microsomal AHH induction, inhibition of body weight gain, and thymic atrophy showed that the potencies of CDF congeners were structure-dependent, and that the *in vivo* structure-activity relationships for the toxic end points closely matched those observed for their *in vitro* AHH induction potencies (Mason et al. 1985). However, CDF congeners containing vicinal unsubstituted carbon atoms deviated from the linear correlation due to *in vivo* metabolism. A similar CDF congeneric pattern of toxicity was found in splenic response assays in C57BL/6 mice (Davis and Safe 1980; Dickerson et al. 1990) and in thymic atrophy and liver hypertrophy in male Wistar rats (Yoshihara et al. 1981) (see Section 2.4). These results, along with results obtained with other halogenated aromatic hydrocarbons (summarized in Safe 1990b), are consistent with and provide support for the common receptor-mediated mechanism of action.

The expression of the toxic response, which is species and strain dependent, is initiated by the binding of individual congeners with the Ah receptor. The responsiveness of a particular organ or cell depends

on the presence of a functional Ah receptor. Initial binding of a CDF congener to the Ah receptor is followed by an activation or transcription step and subsequent accumulation of occupied nuclear receptor complexes. These complexes interact with a specific deoxyribonucleic acid (DNA) sequence in the CYPlAl gene (which regulates the expression of cytochrome P-450IAl isozymes), changing its secondary and supersecondary structure (Elferinck and Whitlock 1990), which leads to enhancement of the CYPlAl gene expression. A specific nucleotide sequence present in multiple copies to which the nuclear complex binds has been identified (Denison et al. 1989). Ultimately, newly synthesized enzymes and macromolecules resulting from the pleiotropic response to the CDF-receptor complex are responsible for many of the effects caused by CDFs and other halogenated aromatic hydrocarbons (see Section 2.4).

2.4 RELEVANCE TO PUBLIC HEALTH

The general population is most likely to be exposed to CDFs by the oral route. Most of the information on human health effects that pertains to CDFs is from studies of people who ingested contaminated rice oil for up to 9-10 months during the Yusho and Yu-Cheng poisoning incidents. These health effects cannot be attributed solely to CDFs due to mixed chemical exposure and possible interactions between CDFs, PCBs, and other components of the contaminated rice oils, but there is sufficient evidence that CDFs are the main causal agents (see Introduction to Section 2.2.2). Although the Yusho and Yu-Cheng studies consist largely of observations on groups that are not very well defined and lack controls and accurate intake data, they do provide a generally consistent picture of the health status of the affected people and an indication of potential effects for the general population who are exposed to low levels of CDFs. Manifestations of the Yusho and Yu-Cheng outbreaks include serious health effects such as severe skin lesions (e.g., persistent acneform eruptions, hyperpigmentation) and ocular signs (e.g., hypersecretion of eyelid glands), increased susceptibility to respiratory infection (e.g., chronic bronchitis), and neurological symptoms and signs (e.g., limb numbness, reduced nerve conduction velocities, delayed neurobehavioral development). Less serious effects observed in Yusho and Yu-Cheng patients include mild hematological changes (e.g., anemia) and clinically insignificant hepatic alterations (e.g., changes in ultrastructure and serum triglycerides). Some of these effects, particularly dermal, ocular, and neurobehavioral manifestations, also occurred in children borne by exposed mothers. Some effects of CDFs in treated animals are consistent with and supportive of the human data, although types and sensitivities of specific end points examined often differed in humans and animals and among animal species, and animals studies may have used near

lethal or lethal doses. Many of the toxicity studies of CDFs in animals have involved acute- or intermediate-duration oral exposure, although one intermediate-duration dermal study is available, and most tested the 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF congeners. Effects of oral CDFs in animals that have not been observed or clearly discerned in exposed humans include moderately severe hepatotoxicity, renal effects, severe body weight loss (wasting syndrome), thymic atrophy, possible testicular toxicity, and developmental effects including hydronephrosis and cleft palate. Some of these changes occurred only at near-lethal levels of exposure, but immunologic effects are particularly sensitive, based on thymic changes in both adult and developing animals at low doses. Few studies have investigated the carcinogenicity of CDFs but there is evidence from the dermal study and parenteral injection studies that CDFs can promote development of tumors initiated by other chemicals.

Limited information on human health effects of probable combined dermal and inhalation exposure to CDFs and other chemicals is available from studies related to an electrical transformer fire in Binghamton (New York) in 1981 (Fitzgerald et al. 1986, 1989; Schecter 1983, 1986, 1987; Schecter and Charles 1991; Schecter and Tiernan 1985; Schecter et al. 1985a, 1985b). Dielectric fluid composed of 65% PCBs (Aroclor 1254) and 35% polychlorinated benzenes was pyrolyzed leading to the formation of a fine, oily soot, which was distributed throughout the building via ventilation shafts. The soot contained high levels PCBs, CDFs, chlorinated dibenzo-*p*-dioxins (CDDs), chlorinated biphenylenes, and other chemicals, including average concentrations of 199 ppm 2,3,7,8-tetraCDF and 3 ppm 2,3,7,8-TCDD, but there was wide variation in the quantification of the contaminants. Firefighters, police officers, cleanup workers, and other personnel were exposed for a few minutes to >l,000 hours (median 8 hours). Medical surveillance was performed on 482 potentially exposed people 9-12 months after the fire, including symptomology and physical examinations of 147 people who were in the building for ≥25 hours (Fitzgerald et al. 1986). Exposure was positively related to mean serum PCB levels, but means and individual values were within the range reported by other studies of people with no unusual exposures. Follow-up health evaluations were performed ≈3 years after exposure (Fitzgerald et al. 1989). More than 96% of the original participants were followed, and loss to follow-up was greatest among people who had either the least potential for exposure or lower mean PCB concentrations. Health effects reported in people exposed during the Binghamton State Office Building incident include frequent coughing, nonspecific gastrointestinal symptoms, muscle pain, mild hepatic effects (e.g., elevated levels of serum liver enzymes, ultrastructural alterations), skin abnormalities (e.g., rashes, acne-like lesions [not chloracne], skin color changes), unintentional weight loss, and neurological symptoms (e.g., numbness in extremities, dizziness) (Fitzgerald et al. 1986,

1989; Schecter et al. 1985a, 1985b). Interpretation of these findings is complicated by low incidences, small sample size, short latency time, unknown exposure levels, intakes that probably were low in most cases, possibility of recall bias, subjective nature of some of the effects, intervening effects of stress, combined routes of exposure, and use of various degrees of protection (air packs, protective clothing) by people with the greatest potential for exposure. Another important study limitation is that all persons who felt they may have had exposure were included, despite no evidence of exposure in many of these persons. Due to the co-exposure to CDFs and other toxic chemicals and lack of confirmed doses of these chemicals, health effects cannot be attributed specifically to CDFs or any of the other components of the soot.

Animal studies show that many of the toxic effects attributable to CDFs, including chloracne, immunotoxicity, inhibition of body weight gain, hepatic changes, and teratogenicity, appear to be mediated by a common mechanism of toxicity that involves a specific cytosolic molecular receptor (Ah receptor) (see Section 2.3.5). Because this mechanism also mediates many of the toxic effects of chlorinated dibenzo-*p*-dioxin (CDD) and PCB congeners, which are structurally similar to CDFs, data on toxicity and related issues (e.g., species differences in sensitivity) for CDDs and PCBs are relevant to CDFs. CDDs and PCBs are evaluated in other ATSDR toxicological profiles (ATSDR 1993, 1994), but selected general data for these chemicals are presented in this section to corroborate effects of CDFs. Numerous factors influence the toxicity of CDFs; some of these factors include differences in absorption, distribution, and retention among animal species (see Section 2.3). However, at the tissue level, the toxic potency for each individual congener is determined by the magnitude of the response that is initiated by the binding of a specific congener with the Ah receptor. As discussed in Section 2.3.5, the binding affinity, in turn, is determined by the substitution pattern of the congener. For many 2,3,7,8-substituted congeners and congeners with less than four lateral substituents, there is a qualitative correlation between their structure-binding and structure-toxicity relationships (Mason et al. 1985). The tissue-specific toxicological effects exhibited by individual CDF congeners (i.e., for 2,3,4,7,8-pentaCDF, a 30-fold difference between ED_{50} values for immunotoxicity and teratogenicity in mice) may not reflect differences in receptor affinity, but rather differences in the battery of enzymes expressed or repressed as a result of the binding with the receptor. Although there is no direct evidence with CDFs to support this view, data with 2,3,7,8-TCDD strongly suggest that this may be the case (Gasiewicz and Rucci 1984). Only a few oral studies have been performed with CDFs other than 2,3,7,8-pentaCDF and 2,3,4,7,8-pentaCDF, but results of these studies indicate that these are among the most toxic congeners. *In vitro* and acute parenteral structure-activity studies, which

typically evaluated sensitive end points such as Ah receptor binding, induction of hepatic microsomal enzymes (e.g., AHH and EROD), body weight loss, and thymic atrophy, and tested a broad spectrum of congeners, have shown that tetra- to hexaCDFs that are fully substituted in the lateral two, three, seven, and eight positions are the most active congeners (Bandiera et al. 1984b; Holcomb et al. 1988; Mason et al. 1985; Safe 1990a; Safe et al. 1986). These studies also indicate that effects of CDFs are generally independent of exposure route. Evaluations of *in vivo* and *in vitro* data for derivation of toxicity equivalent factors (see following paragraph) have shown that 2,3,4,7,8-pentaCDF is more toxic than 2,3,7,8-tetraCDF and other CDF congeners. Additionally, 2,3,7,8-tetraCDF is not expected to be an important contributor to human CDF toxicity because 2,3,7,8-tetraCDF is more rapidly metabolized than the other 2,3,7,8-substituted CDFs (see Section 2.3.3).

People are environmentally exposed to mixtures of halogenated aromatic hydrocarbons, of which various CDFs are constituents, rather than to single CDF congeners. In particular, CDDs frequently occur with CDFs in the environment, and due to the common mechanism of toxicity, total toxicity is from both together. The total toxicity is not necessarily the sum of the total individual congener toxicities since CDFs and CDDs compete for the same receptor and thus, nonadditive behavior may occur. The public and toxicological concerns resulting from exposure to CDFs and structurally related CDDs, as well as the gaps in available information with which to evaluate the human health potential from exposure to CDFs and CDDs, are well recognized (Ahlborg et al. 1992; EPA 1989; McFarland and Clarke 1989; Safe 1990a, 1991). In response to this problem, the EPA Chlorinated Dibenzo-*p*-dioxins/Chlorinated Dibenzofurans Technical Panel of the Risk Assessment Forum recommends an interim method for assisting in estimating the risk from exposure to these chemical mixtures that can be used until the data gaps are filled (Barnes 1991; Bellin and Barnes 1991; EPA 1989). This procedure generates toxicity equivalence factors (TEFs) based on congener-specific data and the assumption that Ah receptor-mediated toxicity is additive. The TEF scheme compares the relative toxicity of individual CDFs and CDDs congeners to that of 2,3,7,8-TCCD, which is the most toxic and extensively studied of these halogenated aromatic hydrocarbons. The TEFs presented in Table 2-3 provide a means of relating toxicity data for CDFs and CDDs, which frequently occur together, to an equivalent level of 2,3,7,8-TCDD. The TEF for 2,3,7,8-TCDD is defined as unity, whereas TEF values for all other CDF and CDD congeners are less than one (zero has been assigned to all non-2,3,7,8-substituted congeners), thus reflecting the lower toxic potency of most CDF and CDD congeners. 2,3,4,7,8-PentaCDF is the most toxic CDF congener with a TEF five times higher than 2,3,7,8-tetraCDF. The TEFs thus generated can be used, assuming additivity of the toxic response, for

TABLE 2-3. Recommended Toxicity Equivalency Factors (TEFs) for CDFs and CDDs[a]

Compound (CDFs)		Compound (CDDs)	
CDFs	EPA current recommended values	CDDs	EPA current recommended values
monoCDFs	0	monoCDDs	0
diCDFs	0	diCDDs	0
triCDFs	0	triCDDs	0
2,3,7,8-tetraCDF	0.1	2,3,7,8-TCDD	1
other tetraCDFs	0	other tetraCDDs	0
1,2,3,7,8-pentaCDF	0.05	2,3,7,8-pentaCDD[b]	0.5
2,3,4,7,8-pentaCDF	0.5	other pentaCDDs	0
other pentaCDFs	0		
2,3,7,8-hexaCDF[b]	0.1	2,3,7,8-hexaCDDs[b]	0.1
other hexaCDFs	0	other hexaCDDs	0
2,3,7,8-heptaCDFs[b]	0.01	2,3,7,8-heptaCDDs[b]	0.01
other heptaCDFs	0	other heptaCDDs	0
octaCDF	0.001	octaCDD	0.001

[a]Derived from EPA 1989
[b]Any isomer that contains chlorine in the 2,3,7,8-positions

CDDs = chlorinated dibenzo-*p*-dioxins; CDFs = chlorinated dibenzofurans; NR = not reported; TEFs = toxicity equivalence factors; TCDD = tetrachlorodibenzo-*p*-dioxin

estimating the toxicity of an environmental mixture containing a known distribution of CDFs and/or CDDs relative to that of 2,3,7,8-TCDD (for further information see Section 2.6). The TEF values will change over time as new toxicity data are obtained. 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 CDDs. The approach is controversial, however, because it is only useful for those congeners which exhibit dioxin-like activity and is not adequately validated (Brown et al. 1992; De Vito et al. 1993; Eadon et al. 1986; Harper et al. 1993; Neubert et al. 1992; Pluess et al. 1988b; Poiger et al. 1989; Safe 1992).

Minimal Risk Levels for CDFs

Inhalation MRLs

No MRLs have been derived for inhalation exposure to CDFs because human and animal data for all durations are lacking.

Oral MRLs

- An MRL of 0.001 μg/kg/day has been derived for acute-duration oral exposure (14 days or less) to 2,3,4,7,8-pentaCDF.

The acute oral MRL was based on a LOAEL for mild thymic lymphoid hypoplasia identified in groups of 6 male Hartley guinea pigs (age 3-4 weeks) that were observed for 30 days following treatment with a single gavage dose of 0, 1, 3, 10, or 30 μg/kg 2,3,4,7,8-pentaCDF in corn oil (Moore et al. 1979). The 3 μg/kg/day dose is the LOAEL as histological examinations were not performed at the lowest dose. The LOAEL is supported by evidence from other studies in guinea pigs, rats, mice, and monkeys that the thymus is a sensitive indicator of immunologic effects of CDFs following acute or intermediate duration oral exposure (Brewster et al. 1988; Kerkvliet et al. 1985; Luster et al. 1979a, 1979b; Moore et al. 1979; McNulty et al. 1981; Oishi and Hiraga 1980; Oishi et al. 1978; Pluess et al. 1988b; Poiger et al. 1989). Thymic atrophic changes manifested as histologic alterations and/or decreased organ weight were characteristic effects in these studies.

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- An MRL of 0.00003 µg/kg/day has been derived for intermediate-duration oral exposure (15-364 days) to 2,3,4,7,8pentaCDF.

The intermediate oral MRL was based on a LOAEL for hepatic effects (increased serum bilirubin, decreased serum triglycerides) identified in groups of six male and six female 1va:SIVSO (SD) rats (age ≈7 weeks) that were fed diets providing estimated dosages of 0, 0.1, 1, or 10 pg/kg/day for 13 weeks (Pluess et al. 1988a; Poiger et al. 1989). The LOAEL of 0.1 µg/kg/day is supported by evidence from other animal studies that the liver is a target of CDFs following acute- and intermediate-duration oral exposure (Ahlborg et al. 1989; Brewster et al. 1988; Doyle and Fries 1986; McNulty et al. 1981; Moore et al. 1979; Oishi and Hiraga 1978; Oishi et al. 1978; Pluess et al. 1988b; Poiger et al. 1989). Typical hepatic changes observed primarily in rats and monkeys include microsomal enzyme induction, increased serum enzyme levels and liver weight, altered serum cholesterol and triglycerides, fatty and/or necrotic changes in the liver, and bile duct epithelial hyperplasia.

The acute- and intermediate-duration MRLs discussed above are for 2,3,4,7,8-pentaCDF, which is more toxic than some other CDF congeners. Therefore, applying these MRLs to other CDFs may lead to overestimating actual risks.

An MRL for chronic-duration oral exposure was not derived for CDFs because human and animal data are lacking for this exposure category.

Death. Limited information is available on mortality in humans exposed to CDFs. An epidemiological study of the Yusho incident showed no increased noncancer mortality and an inconclusive increase in liver cancer mortality (Kuratsune et al. 1987). Deaths occurred in ≈1% of Yu-Cheng victims, apparently due to nonmalignant or malignant liver disease in half the cases (Hsu et al. 1985), but comparison rates were not reported. Data from these studies are insufficient for determining if low level exposure to CDFs by oral or other routes is likely to cause death in humans.

Oral studies in animals indicate that CDFs are extremely toxic, causing death in the ug/kg range after acute and intermediate duration exposure (Brewster et al. 1988; Ioannou et al. 1983; Moore et al. 1976, 1979; Pluess et al. 1988a, 1988b; Poiger et al. 1989). The guinea pig and monkey are especially sensitive species and congeners substituted in the 2,3,7,8-positions, particularly 2,3,4,7,8-pentaCDF and

2,3,7,8-tetraCDF, are most toxic. Animals usually do not die for many days following exposure to a single oral dose of CDFs (30-day observation periods are common in lethality assays), indicating that delayed toxicity may be a concern in acutely exposed humans. Acute and subchronic gavage studies with guinea pigs suggest that total dose administered may be a more important determinant of lethality than size of a single dose or frequency of exposure (Luster et al. 1979a, 1979b; Moore et al. 1979). Death was usually preceded by a weight loss (wasting syndrome), but insufficient information is available to determine the cause of death. An intermediate duration dermal exposure study showed that 1,2,3,4,7,8-hexaCDF was more toxic than 2,3,4,7,8-pentaCDF in mice when applied in acetone vehicle (Hebert et al. 1990). Insufficient information is available for these isomers to compare dermal and oral toxicity, but dermal absorption is likely to be less than half of oral absorption (see Section 2.3.1) and dermal absorption from acetone vehicle is likely to be much higher than from soil. The deaths observed in animals orally or dermally exposed to CDFs suggest that death could also occur in humans if exposure is high enough.

Systemic Effects

Respiratory Effects. Chronic bronchitis and related effects (e.g., cough, expectoration) were observed in many Yusho and Yu-Cheng patients (Kuratsune 1989; Nakanishi et al. 1985; Rogan 1989; Shigematsu et al. 1971, 1977). The bronchitis, which was generally attributed to severe respiratory infection resulting from lowered resistance to illness (i.e., secondary to immunological effects), differed from usual bronchitis (e.g., no crackles) and only gradually improved following exposure. No pulmonary histological changes developed, however, in animals that were treated with single nonlethal (guinea pigs, mice) or lethal (guinea pigs, rats) doses of 2,3,4,7,8-pentaCDF or 2,3,7,8-tetraCDF .(Brewster et al. 1988; Moore et al. 1979). Information on respiratory effects of CDFs in animals after intermediate or chronic duration exposure is not available. Interpretation of the human data is complicated by co-exposure to PCBs, although there is evidence that PCBs and CDDs can induce respiratory effects (ATSDR 1993, 1994), and the lack of longer duration animal studies. The existing data indicate a potential for respiratory effects in humans exposed to CDFs when exposure levels are high enough.

Cardiovascular Effects. No information is available on cardiovascular effects of CDFs in humans. Hemorrhages occurred under the nails of rats, in the stomach of monkeys, and in the adrenals of guinea pigs given single lethal oral doses of 2,3,7,8-tetraCDF and/or 2,3,4,7,8-pentaCDF (Brewster et

al. 1988; Moore et al. 1979). This is suggestive of a general hemorrhagic effect in dying animals. Histology of the heart was normal in animals that were treated with single nonlethal (guinea pigs, mice) or lethal (guinea pigs, rats) gavage doses of 2,3,4,7&pentaCDF or 2,3,7,8-tetraCDF (Brewster et al. 1988; Moore et al. 1979). Similarly, cardiac histology was not altered in rats fed nonlethal doses of 1,2,3,7,8-pentaCDF, 1,2,3,4,8-pentaCDF or 1,2,3,6,7,8-hexaCDF, or a lethal dose of 2,3,4,7,8-pentaCDF, for 13 weeks (Pluess et al. 1988a, 1988b; Poiger et al. 1989). Chronic studies have not been performed and there is no information on effects of CDFs on cardiovascular function, although 2,3,7,8-substituted CDDs can induce cardiovascular effects (ATSDR 1994). Based on the available information, it is not known whether populations exposed to CDFs near hazardous waste sites may develop cardiovascular effects. It has been suggested that hemorrhages observed in animals exposed to CDFs and related halogenated aromatic compounds are due to impaired clotting, resulting from decreased numbers of platelets, but there are few data in support of this mechanism (McConnell 1989).

Gastrointestinal Effects. No information was located regarding gastrointestinal effects of CDFs in humans other than symptoms such as vomiting and diarrhea following exposure during the Yusho incident (Kuratsune 1989). Gastrointestinal tract histology was normal in some animal species that were administered single nonlethal (guinea pigs, mice) or lethal (guinea pigs) gavage doses of 2,3,4,7,8-pentaCDF or 2,3,7,8-tetraCDF (Moore et al. 1979). However, near-lethal or lethal single gavage doses of these congeners produced gastric effects in rats (epithelial hyperplasia) and monkeys (e.g, focal ulceration and mucosal cysts) (Brewster et al. 1988; Moore et al. 1979). Similar gastric changes also occurred at lethal doses in intermediate duration diet studies with 2,3,7,8-tetraCDF in monkeys (mucosal cysts) (McNulty et al. 1981) and 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF in dermal studies with mice (mucous cell hyperplasia) (Hebert et al. 1990). Gastrointestinal effects, including mucosal changes that progress to stomach ulcerations and hemorrhages, are also common in monkeys after exposure to 2,3,7,8-TCDD or PCBs (ATSDR 1993, 1994), suggesting that primates may be particularly susceptible to CDF-induced gastrointestinal toxicity. No specific information on mechanism(s) was located. The animal data suggest, however, that the symptoms reported by Yusho patients could possibly reflect a direct gastrointestinal effect of 2,3,7,8-substituted CDFs rather than central nervous system or general toxicity of CDFs, and indicate that there is a possibility of gastrointestinal effects occurring in populations exposed to CDFs near hazardous waste sites.

2. HEALTH EFFECTS

Hematological Effects. Mild normocytic anemia and leukocytosis are fairly consistent findings in Yu-Cheng patients (Rogan 1989). Alterations indicative of mild anemia (decreased hemoglobin concentration with generally unchanged red blood cell count) are the only hematological effects consistently observed in animals exposed to CDFs. Alterations have been observed in single dose studies with 2,3,4,7,8-pentaCDF or 2,3,7,8-tetraCDF in rats, mice, and monkeys (not in guinea pigs), and in intermediate-duration studies with 2,3,4,7,8-pentaCDF, 1,2,3,7,8-pentaCDF or 1,2,3,6,7,8-hexaCDF in rats, but not with 2,3,7,8-tetraCDF in mice, guinea pigs, or monkeys (Brewster et al. 1988; Luster et al. 1979a, 1979b; McNulty et al. 1981; Moore et al. 1979; Pluess et al. 1988a, 1988b; Poiger et al. 1989). Intermediate-duration exposure to a mixture of various tetra-, penta-, and hexaCDF caused hemolytic anemia in rats (Oishi and Hiraga 1978; Oishi et al. 1978). Insufficient information is available to explain the variations in response, but total doses of each congener could be a factor, as studies with related halogenated aromatic compounds indicate that anemia is related to dose-level and duration of exposure (McConnell 1989). Studies with 2,3,7,8-TCDD indicate that monkeys may be highly sensitive to hematological effects of CDFs (ATSDR 1994). No treatment-related hematologic alterations occurred in the only animal study of a non-2,3,7,8-substituted CDF congener (1,2,3,4,8-pentaCDF in rats) (Pluess et al. 1988b; Poiger et al. 1989). Anemia observed in animals exposed to CDFs and related halogenated aromatics has been postulated to be due to toxic effects on erythropoiesis (McConnell 1989). The available evidence indicates that it is possible that hematological effects can occur in populations exposed to 2,3,7,8-substituted CDFs near hazardous waste sites.

Musculoskeletal Effects. Musculoskeletal effects have not been reported in Yusho or Yu-Cheng victims (Kuratsune 1989; Rogan 1989). Reduced muscle mass with no altered muscle histology was observed in guinea pigs following single gavage doses of 2,3,7,8-tetraCDF or 2,3,4,7,8-pentaCDF (Moore et al. 1979), but this is likely a manifestation of the general wasting syndrome. The animal data, therefore, provide an insufficient basis for assessing if the musculoskeletal system is a potential target of CDFs.

Hepatic Effects. The liver is a target organ of CDFs in humans and animals. Various hepatic effects have been observed in humans exposed during Yusho, but increased SGOT and SGPT levels, increased serum triglycerides with unchanged serum cholesterol and increased urinary excretion of uroporphyrin appear to be the most consistent changes (Chang et al. 1980; Gladen et al. 1988; Kuratsune 1989; Lu et al. 1980; Okumura et al. 1979; Rogan 1989; Uzawa et al. 1969). A marked

elevation in serum triglycerides is one of the few abnormal findings peculiar to Yusho and Yu-Cheng, but the mechanism of the increase is unknown (Kuratsune 1989; Rogan 1989). Ultrastructural changes, particularly endoplasmic reticulum alterations probably indicative of microsomal MFO enzyme induction and mitochondrial alterations, appear to be the predominant hepatic morphological finding in Yusho patients. There is no evidence that the above hepatic effects observed in humans are clinically significant.

CDFs have induced generally similar spectra of mild to moderate hepatic effects in animals following single dose or intermediate duration oral exposures. Typical changes observed primarily in rats and monkeys included hepatic microsomal enzyme induction, increased serum enzyme levels and liver weight, altered serum cholesterol and triglycerides, fatty and/or necrotic changes in the liver, and bile duct epithelial hyperplasia (Ahlborg et al. 1989; Brewster et al. 1988; Doyle and Fries 1986; Moore et al. 1979; McNulty et al, 1981; Oishi and Hiraga 1978; Oishi et al. 1978; Pluess et al. 1988a, 1988b; Poiger et al. 1989). Tetra-, penta-, and hexaCDF congeners substituted in the 2,3,7,8 positions were more hepatotoxic than congeners not substituted in these positions. This pattern of toxicity has also been demonstrated in acute intraperitoneal and *in vitro* structure-activity relationship studies that evaluated induction of hepatic microsomal MFO enzymes (e.g., AHH, EROD) in rats (Bandiera et al. 1984b; Holcomb et al. 1988; Mason et al. 1985; Safe et al. 1986). As discussed in Section 2.3.5, structure-activity relationships for the induction response are comparable to structure-Ah receptor binding relationships, and the inductive potency *in vitro* correlates well with that observed *in vivo.* These and other findings strongly indicate that induction of certain cytochrome P-450IA-dependent microsomal MFO enzymes by CDFs, including AHH and EROD, is mediated by the Ah receptor. Although induction of these enzymes is a characteristic effect of CDFs and related compounds and indicates that interaction with the Ah receptor occurred, it does not necessarily indicate that hepatotoxic effects will also occur (Poland and Knutson 1982). Based on studies with 2,3,7,8-TCDD and PCBs, there is some evidence that effects of CDFs on lipids (increased serum triglycerides and cholesterol, fatty infiltration of liver) may be Ah receptor-mediated and related to alterations in synthesis of apoproteins involved in lipid formation and utilization (Goldstein and Safe 1989). The extrahepatic biliary epithelial effects may be related to elimination of CDFs and metabolites in the bile (McConnell 1989). The lowest intermediate duration dose observed to cause hepatic effects was 0.1 μg/kg/day 2,3,4,7,8-pentaCDF, which increased serum bilirubin and decreased serum triglycerides in rats (Pluess et al. 1988a; Poiger et al. 1989). This LOAEL is used as the basis for an intermediate-duration MRL for oral exposure and also caused decreased thymus weight in rats (see Immunological

Effects). Intermediate-duration dermal exposure to 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF induced increased relative liver weight and liver hypertrophy in mice (Hebert et al. 1990). Since there is suggestive human and conclusive animal evidence that the liver is a target organ of CDFs by different routes of exposure, it is possible that hepatic effects can occur at sufficiently high exposure levels in populations exposed to CDFs near hazardous waste sites.

Renal Effects. No effects on the kidney have been reported in humans exposed during the Yusho or Yu-Cheng incidents (Kuratsune 1989; Rogan 1989). Renal toxicity of CDFs in animals was investigated in several oral studies which found changes only at acute lethal levels of 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF (Brewster et al. 1988; Moore et al. 1979). Effects included increased blood urea nitrogen and/or hyperplasia of the renal pelvis, ureter, and bladder in guinea pigs, rats, or monkeys. Hyperplasia was not observed in rats, which is consistent with studies of related chlorinated halogenated compounds (McConnell 1989). Based on these studies, it has been postulated that the hyperplastic responses may be related to species differences in the rate and route of elimination of these chemicals from the body (i.e., proportion of a given dose excreted via urine). Developing kidneys are also a target of CDFs as shown by an alteration in the ureteral epithelium (hydronephrosis) in mice induced by *in utero* exposure to CDFs (see Developmental Effects). The animal data suggest that there is a possibility that mild renal and urinary tract effects could develop in humans if exposure is high enough.

Dermal/Ocular Effects. Effects in the skin and eyes were the most obvious and frequent manifestations of toxicity following oral exposure during the Yusho and Yu-Cheng incidents (Fu 1984; Kuratsune 1989; Lu and Wu 1985; Rogan 1989). Characteristic skin changes included follicular plugging in pilosebaceous orifices, acneform eruptions, dark colored pigmentation frequently in the gingival and buccal mucosa, lips and nails, and deformed nails. Skin abnormalities include acne-like lesions (not chloracne). Examinations 16 years after the Yusho outbreak showed that more than half of the patients still exhibited some dermal signs (Toshitani et al. 1985). Eye discharge and other severe ocular effects occurred during the acute phase of the Yusho and Yu-Cheng syndrome, such as meibomian gland (eyelid) changes including enlargement, irritation and hypersecretion, and abnormal pigmentation of the conjunctivae and eyelids. Improvement of the dermal and ocular effects was gradual, apparently because of slow release of CDFs from body adipose stores. Of 75 Yusho patients examined ≈l0 years after the outbreak, 84% and 43% still showed abnormal changes in the Meibomian glands (e.g., atrophy, secretion) and pigmentation of the conjunctivae and eyelids,

respectively (Kono and Yamana 1979). Considering an estimated elimination half-life of 1.5 years for two toxic congeners that were preferentially retained in Yu-Cheng patients (Ryan et al. 1990), it is evident that persistent dermal and ocular effects are associated with small body burdens of CDFs.

Average body burdens of CDFs associated with chloracne in Yusho and Yu-Cheng victims have been estimated (Ryan et al. 1990). Using Yusho oil consumption data and assuming a clearance half-life of 1.5 years for the two most toxic congeners (2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF), the body burden associated with chloracne in Yusho victims was estimated as 5.9 μg/kg expressed as a 2,3,4,7,8-pentaCDF equivalent (PEQ) amount. This is somewhat higher than a body burden of 4.4 μg PEQ/kg estimated to produce the first clinical signs of Yusho illness (nausea and anorexia). Using measured blood levels of CDFs in Yu-Cheng victims with chloracne and assuming 2,3,4,7,8-pentaCDF:1,2,3,4,7,8-hexaCDF ratios of 1:l in blood and 5:l for relative toxicity, the body burden associated with chloracne in Yu-Cheng victims was estimated as 4.0 μg PEQ/kg. Using a TEF-based analysis, this Yu-Cheng body burden was shown to be comparable to adipose tissue levels of 2,3,7,8-TCDD known to cause chloracne in monkeys. The TEF principle is discussed in the introduction to Section 2.4.

Single-dose and intermediate-duration oral studies have shown dermal and ocular effects in monkeys exposed to 2,3,7,8-tetraCDF, but not in guinea pigs exposed to 2,3,7,8-tetraCDF or 2,3,4,7,8-pentaCDF (McNulty et al. 1981; Moore et al. 1979). Effects were progressive, dose-related, and consistent with those observed in Yusho and Yu-Cheng victims, including facial and periorbital edema, exudate and occlusion of meibomian and ceruminous (ear canal) glands, hyperkeratotic sebaceous gland ducts, follicular orifices and nail beds, and loss of facial and body hair and nails. Monkeys also have been shown to be very sensitive to similar dermal effects induced by oral exposure to 2,3,7,8-TCDD or PCBs (ATSDR 1993, 1994). Skin changes also developed in mice that were dermally treated with a single dose of tumor initiator (MNNG) followed by intermediate duration application of 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF (Hebert et al. 1990). These included epidermal hyperplasia, squamous metaplasia of sebaceous glands, inflammation of dermis, and atrophy or loss of hair follicles and sebaceous glands. Although application of CDFs without initiator was not performed and acetone vehicle was used, these dermal effects are generally consistent with those observed in oral studies of CDFs.

2. HEALTH EFFECTS

Based on studies of 2,3,7,8-TCDD and PCBs, there appears to be a common systemic mechanism for many of the dermal and ocular manifestations of CDFs. Chloracne starts with formation of keratin plugs in the pilosebaceous orifices and inflammatory folliculitis. The folliculitis stimulates keratinization of the sebaceous gland ducts and outer root sheath of the hair, leading to formation of keratin cysts (Emmett 1986). The pathology of swollen eyelids is due to keratinization of the Meibomian gland, which is homologous with chloracne.

In conclusion, there is strong human and animal evidence indicating that dermal effects are likely to occur in people exposed to CDFs in the vicinity of hazardous waste sites if levels are high enough.

Other Systemic Effects. Animal studies provide conclusive evidence that oral exposure to CDFs causes a wasting syndrome characterized by progressive decreased weight gain, with immediate moderate to severe body weight loss generally preceding death (Brewster et al. 1988; Kunita et al. 1984; Luster et al. 1979a, 1979b; Moore et al. 1976, 1979; Oishi et al. 1978; Pluess et al. 1988a, 1988b; Poiger et al. 1989). Wasting was observed with 2,3,7,8-substituted tetra-, penta-, and hexaCDF congeners in single dose and intermediate duration oral studies with guinea pigs, rats, and monkeys. Decreased weight gain and weight loss also occurred in mice that were dermally treated with 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF for 20 weeks (Hebert et al. 1990). Structure-activity studies in which CDFs were administered to rats by a single intraperitoneal injection have also demonstrated that the tetra- to hexaCDF congeners, which are fully substituted in the lateral two, three, seven, and eight positions are most active in inhibiting body weight gain (Bandiera et al. 1984b; Holcomb et al. 1988; Mason et al. 1985; Safe et al. 1986). Information on body weight changes has not been reported for Yusho and Yu-Cheng patients (Kuratsune 1989; Rogan 1989), except for decreased birth weights (see Developmental Effects). Animal and human evidence therefore indicates that the wasting syndrome is independent of exposure route. The mechanism of the wasting syndrome has been extensively investigated in animals treated with 2,3,7,8-TCCD but, although basically linked to Ah-receptor binding (see Section 2.3.5), is not clearly understood (ATSDR 1994). Evidence indicates that some other factor(s) than decreased food or water consumption contributes to the weight loss. The mechanism of wasting may be related to effects on thyroid hormones that regulate fat mobilization and utilization of fatty acids in adipose tissue, influence norepinephrine-mediated, nonshivering thermogenesis, or cause anorexia (Rozman et al. 1985; Pazdernik and Rozman 1985; Aust 1984). Appetite suppression due to increased levels of tryptophan in the hypothalamus may also be involved in the wasting syndrome (Rozman et al. 1991; Weber et al. 1991a, 1991b). Tryptophan is

a precursor of the neurotransmitter serotonin. Elevated tryptophan levels, which cause increased serotonin release in the brain, are due to reduced gluconeogenesis, probably resulting from inhibition of phosphoenolpyruvate carboxykinase (a regulatory enzyme in gluconeogenesis). Although the wasting syndrome is a characteristic effect of CDFs in animals usually associated with lethality, it is possible that body weight changes could occur in people exposed to sufficiently high levels.

There is some evidence that the adrenal gland may be a target of CDFs. Studies of Yusho victims showed increased urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids (Nagai et al. 1971). Single lethal doses of 2,3,7,8-tetraCDF or 2,3,4,7,8-pentaCDF caused adrenal hemorrhage in guinea pigs, but a lethal dosage of 2,3,7,8-tetraCDF in an intermediate duration study produced no consistent change in serum hydrocortisone levels (Luster et al. 1979a, 1979b; Moore et al. 1979). Increased levels of corticosteroids are not good indicators of adrenal toxicity because they can be caused by adrenal stimulation due to stress or diseases. Reduced adrenal function has been observed in animals exposed to 2,3,7,8-TCDD or PCBs, apparently due in part to decreased corticosterone synthesis from decreased adrenal cholesterol side-chain cleavage and 21-hydroxylation of progesterone (ATSDR 1993, 1994; Goldstein and Safe 1989). The available data suggest that the adrenal may be a possible target of CDFs.

Immunological Effects. Clinical observations of increased susceptibility to respiratory and dermal infections and various changes in immune parameters, including decreased antibody and leukocyte levels and delayed-type skin hypersensitive response, have been observed in Yusho and Yu-Cheng victims (Chang et al. 1981, 1982a, 1982b; Kuratsune 1989; Lu and Wu 1985; Nakanishi et al. 1985; Rogan 1989; Shigematsu et al. 1971). Studies in animals indicate that the immunological system may be the most sensitive to effects caused by CDFs. Pronounced decreases in thymus weight and/or histologic thymic atrophy have been consistently observed following oral exposure in all tested species, including offspring of rats exposed during gestation (see Developmental Effects). Histological changes were occasionally reported in spleen (e.g., hypocellularity of lymphoid elements) and lymph nodes (atrophic changes). Immune system tissues other than thymus were not routinely examined because studies with CDDs suggested that the thymus would be a sensitive target organ for CDFs. Single doses ≤3 μg/kg 2,3,4,7,8-pentaCDF and 5 μg/kg/day 2,3,7,8-tetraCDF induced thymic changes in guinea pigs (Moore et al. 1979). The 3 μg/kg/day LOAEL is used as the basis for an acute-duration MRL for oral exposure. This dose also caused reduced muscle mass in guinea pigs (see Musculoskeletal Effects). In intermediate duration oral studies, effects on thymus weight and histology

were induced at dosages ≥0.1 μg/kg/day 2,3,4,7,8-pentaCDF in rats (Pluess et al. 1988a; Poiger et al. 1989), 0.5 μg/kg/day 2,3,7,8-tetraCDF in guinea pigs (Luster et al. 1979a, 1979b), and 2.1 μg/kg/day 2,3,7,8-tetraCDF in monkeys (McNulty et al. 1981). Decreased thymus and spleen weights with atrophy were found in mice dermally exposed to 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF (Hebert et al. 1990).

CDFs substituted in the 2,3,7,8 positions are more immunotoxic than congeners without full lateral substitution and 2,3,4,7,8-pentaCDF appears to be most immunotoxic. For example, 13-week diet studies in mice showed LOAELs of 0.1, 1, 10 and >300 for 2,3,4,7,8-pentaCDF, 1,2,3,6,7,8-hexaCDF, 1,2,3,7,8-pentaCDF, and 1,2,3,4,8-pentaCDF, respectively (Pluess et al. 1988a, 1988b; Poiger et al. 1989). This pattern of toxicity is illustrated by effective doses for decreased splenic response to sheep red blood cells in mice. Mice given a single intraperitoneal injection of 2,3,4,7,8-pentaCDF, 2,3,7,8-tetraCDF, 1,2,3,7,9-pentaCDF, or 1,3,6,8-tetraCDF had estimated ED_{50} values of 1, 4.3, 241.4, and 10,924 μg/kg/day, respectively, for the splenic response (Davis and Safe, 1988). Estimated ED_{50} values for the splenic response in mice administered 10 intraperitoneal doses of heptaCDF congeners in 12 days were 4,499, 4,908, 490,800, and 613,500 μg/kg/day for 1,2,3,4,6,7,8-heptaCDF, 1,2,3,4,7,8,9-heptaCDF, 1,2,3,4,6,7,9-heptaCDF, and 1,2,3,4,6,8,9-heptaCDF, respectively (Dickerson et al. 1990). The same congeneric pattern of activity has also been observed for thymus weight decrease in rats following a single intraperitoneal injection of CDFs (Bandiera et al. 1984b; Mason et al. 1985; Safe et al. 1986). In the only oral study that investigated suppression of the splenic response to sheep red blood eels, the ED_{50} for a single dose of 1,2,3,4,6,7,8-heptaCDF was estimated to be 208 μg/kg in mice (Kerkvliet et al. 1985).

Effects of CDFs on immunocompetence have been evaluated in two intermediate duration oral studies. Macrophage inhibition index and proliferation of lymphocytes following *in vitro* stimulation with a T-lymphocyte mitogen (phytohemagglutinin) decreased in guinea pigs following intermediate duration exposure to 2,3,7,8-tetraCDF (Luster et al. 1979a, 1979b). A study of mortality in mice treated with an uncharacterized mixture of 88% pentaCDFs and 12% tetraCDFs and subsequently challenged with a bacterial endotoxin (*E. coli* lipopolysaccharide) were inconclusive (Oishi and Hiraga 1980). Although these data are only suggestive of functional alterations in immune response, it is likely that altered function is part of the spectrum of immunological effects of CDFs. The immunotoxicity of CDFs, CDDs, and PCBs appears to be associated with binding to the Ah receptor (Section 2.3.5) (Harper et al. 1993; Vos and Luster 1989). This receptor has been identified in various tissues, including human

and murine lymphocytes, thymic epithelial cells, and bone marrow cells. Thymic atrophy and suppressed antibody responses, induced by CDF, 2,3,7,8-TCDD, and/or PCB congeners, have been shown to be Ah receptor-mediated. Although there is evidence that the immunotoxicity of CDFs and related chlorinated aromatic compounds is associated with the Ah receptor, the mechanisms responsible for toxicity following interaction of the receptor-ligand complex with the Ah locus are unknown (Vos and Luster 1989). There is some evidence that additional loci may be involved and that these compounds can directly affect the thymic epithelium, leading to thymic atrophy and suppression of cell-mediated immunity.

The lowest dose of 2,3,4,7,8-pentaCDF producing thymic changes in rats (0.1 μg/kg/day) (Pluess et al. 1988a; Poiger et al. 1989) is lower than LOAELs for systemic and nonhepatic effects in other intermediate duration studies. However, the immune system is likely to be more sensitive than the liver. As discussed in Developmental Effects, evidence of thymic toxicity has also been observed in offspring of exposed rats. The animal studies clearly show that immunotoxicity is one of the major and most sensitive effects of CDFs and this is supported by some human data. Therefore, there is a possibility that exposure to CDFs around hazardous waste sites could produce immunological effects in humans.

Neurological Effects. Studies of people exposed during the Yusho and Yu-Cheng incidents showed that various neurological symptoms were common, including numbness, weakness, and neuralgia of limbs and hypesthesia, as well indications of reduced sensory and motor nerve conduction velocities (Chen et al. 1985a; Chia and Chu 1984, 1985; Kuratsune 1989; Kuroiwa et al. 1969; Rogan 1989). No information is available on the mechanism of the reduced nerve conduction velocities (e.g., loss of myelin). There is evidence of delayed neurobehavioral development in children born to mothers with Yu-Cheng exposure (Rogan et al. 1988; Yu et al. 1991). Studies of animals orally treated with CDFs provide no definitive conclusions on possible neurobehavioral toxicity because sensitive neurological tests were not performed. Rats given single lethal doses of 2,3,4,7,8-pentaCDF displayed nonspecific signs of toxicity, including piloerection and splayed and hunched posture. Intermediate duration administration of sublethal dosages of a tetra-, penta-, and hexaCDF mixture caused grossly observable cerebral edema and flabby brain appearance in rats (Brewster et al. 1988; Oishi et al. 1978). Single lethal doses of 2,3,4,7,8-pentaCDF or 2,3,7,8-tetraCDF did not alter brain histology in guinea pigs and mice (Moore et al. 1979). The findings in the animal studies are not indicative of the presence or absence of neurological effects and could be secondary to other changes occurring in intoxicated or

dying animals. There is evidence that CDDs caused peripheral neuropathy and other neurological effects in humans and minor alterations in brain neurotransmitters in animals (ATSDR 1994). The available evidence thus provides some indication that the nervous system is a potential target of CDF toxicity and that some types of neurological effects could occur in populations around waste sites if levels of CDFs were high enough.

Reproductive Effects. Irregular menstrual cycles, abnormal basal body temperature patterns, and decreased urinary excretion of estrogens, pregnanediol, and pregnanetriol were observed in female Yusho patients (Kusuda 1971). These alterations suggested possible corpus luteum insufficiency and retarded follicular maturation. Fertility, fecundity, and rates of spontaneous abortion, however, have not been studied in either Yu-Cheng or Yusho patients (Kuratsune 1989; Rogan 1989). Histology of the ovaries, uterus, and testes was normal in rats orally exposed to 1,2,3,7,8-pentaCDF, 2,3,4,7,8-pentaCDF, 1,2,3,4,8-pentaCDF, or 1,2,3,6,7,8-hexaCDF in an intermediate duration study (Pluess et al. 1988a, 1988b; Poiger et al. 1989). A single 80 µg/kg intraperitoneal dose of 2,3,4,7,8-pentaCDF caused significantly reduced uterine peroxidase activity and uterine wet weight in 25-day-old Sprague-Dawley rats (Astroff and Safe 1990). Antiestrogenic effects of 2,3,7,8-tetraCDF, 2,3,4,7,8-pentaCDF, 6-alkylated-1,2,3-trichlorodibenzofurans, and 2,3,7,8-TCDD in rats, mice, and/or human breast cancer cell lines have also been reported (Astroff and Safe 1988, 1990, 1991; ATSDR 1994; Krishnan and Safe 1993; Zacharewski et al. 1992), and 2,3,7,8-TCDD induces decreased fertility and other reproductive effects in female rodents and monkeys (ATSDR 1994). A single dose study with 2,3,4,7,8-pentaCDF caused no testicular histologic changes in rats (Brewster et al. 1988), although intermediate duration exposure to a mixture of tetra-, penta-, and hexaCDFs decreased seminal vesicle and ventral prostate weights and testicular testosterone concentrations in this species (Oishi et al. 1978). Additionally, a single oral dose of 2,3,4,7,8-pentaCDF or 2,3,7,8-tetraCDF caused hypocellularity of the seminiferous tubules in guinea pigs (Moore et al. 1979). The biological significance of the testicular changes induced by the CDFs is uncertain because reproductive function was not assessed. However, androgenic effects also occurred in rats orally treated with 2,3,7,8-TCDD, including reduced serum testosterone and dihydrotestosterone levels and reduced spermatogenesis (ATSDR 1993). Studies with 2,3,7,8-TCDD suggest that androgenic deficiency may be due to decreased androgen synthesis and that altered testicular morphology may be due to changes in lipid peroxidation (ATSDR 1994; Goldstein and Safe 1989). Although there is no conclusive evidence that CDFs cause reproductive effects in humans, the findings in male animals suggest that effects may

occur. This information is important for populations residing near hazardous waste sites who may be exposed to CDFs for a long period of time.

Developmental Effects. Various signs of toxicity have been observed in children born to mothers exposed during the Yusho and Yu-Cheng incidents (Funatsu et al. 1971; Gladen et al. 1988, 1990; Hsu et al. 1985; Lan et al. 1987; Rogan et al. 1988; Rogan, 1989; Taki et al. 1969; Yamaguchi et al. 1971; Yoshimura 1974; Yu et al. 1991). Toxic effects include dermal lesions similar to those found in exposed adults, perinatal deaths in some babies with dermal lesions, decreased birth weights, and neurobehavioral deficits. No exposure-related congenital malformations have been reported in children born to Yusho or Yu-Cheng mothers. It is well documented that orally administered 2,3,7,8-substituted tetra-, penta-, and hexaCDF congeners induce hydronephrosis and cleft palate in mice at doses that are not maternotoxic and that hydronephrosis is induced at lower doses than cleft palate (Bimbaum et al. 1987a, 1987b; Weber et al. 1984, 1985). The kidney and palate were the only tissues examined in mice because studies with 2,3,7,8-TCDD showed that morphogenesis in these tissues is selectively affected (ATSDR 1994). The strain of mouse (C57BL/6N) tested in these oral studies is known to be Ah-responsive (Morrissey and Schwetz 1989), and a single intraperitoneal dose of 0.6 mg/kg 2,3,7,8-tetraCDF on day 12 of gestation induced high incidences of cleft palate and hydronephrosis in Ah-responsive inbred mouse strains, but no cleft palates and few fetuses with hydronephrosis in Ah-nonresponsive strains (Hassoun et al. 1984). Ah-nonresponsive mice appear to have a defective Ah receptor (Goldstein and Safe 1989). This evidence and studies of 2,3,7,8-TCDD (ATSDR 1994; Morrissey and Schwetz 1989) indicate that developmental toxicity of CDFs is mediated by the Ah receptor (see Section 2.3.5). Studies with 2,3,7,8-TCDD indicate that the *in utero* development of hydronephrosis induced by CDFs may be caused by hyperplasia of the ureteral epithelium (Abbot et al. 1987). Both 2,3,4,7,8-pentaCDF and 2,3,7,8-TCDD have been shown to cause hemorrhages in placental tissues (embryo-maternal vascular barrier, visceral yolk sac membrane, maternal vascular spaces of the placenta periphery) of mice at teratogenic doses (Khera 1992). It is not known, however, if these hemorrhagic lesions play a role in the induction of cleft palate or hydronephrosis. Studies of 2,3,4,7,8-pentaCDF in rats have shown induction of hydronephrosis but, no cleft palate, at fetolethal doses, and evidence of thymus toxicity at doses lower than those inducing hydronephrosis in rats or mice (Couture et al. 1989; Masden and Larsden 1989). The lowest doses producing decreased thymus weight occurred in rat offspring examined at age 1 week, and an accompanying cross-fostering experiment showed that *in utero* and lactation exposure contributed almost equally to the effect. This indicates that the immune system is a more sensitive developmental

end point than either hydronephrosis or cleft palate. Considering the reports in humans and strong evidence from animal studies indicating developmental toxicity of CDFs, the possibility that developmental effects may occur in humans exposed to sufficient levels of CDFs around hazardous waste sites cannot be dismissed.

Genotoxic Effects. Limited information was located regarding genotoxic effects of CDFs in humans or animals. As indicated in Section 2.2, the frequency of sister chromatid exchanges increased in subjects exposed orally to CDFs and PCBs compared to control subjects (Lundgren et al. 1988). It should be noted, however, that there was no correlation between serum levels of CDF congeners and increases in sister chromatid exchange frequency. The investigators explained that this lack of correlation was possibly due to the fact that the concentration of PCBs in serum from these individuals was 1,000 times higher than that of CDFs, and to the fact that great daily variations exist in the tissue/blood concentration ratios of CDFs, compared to PCBs.

The mutagenicity of several CDF congeners has been evaluated in microorganisms. In assays with *Salmonella typhimurium* bacteria, octaCDF and 2,3,7,8-tetraCDF were not mutagenic in strains TA98, TA100, TA1535, TA1537, and TA1978 (Schoeny 1982). In addition, octaCDF was not mutagenic in strains TA92, TS24, TA2322, and TA2637. These assays were conducted with and without a metabolic activating system derived from rat liver. Testing of the four monochlorinated dibenzofurans in *S. typhimurium* TA98 and TA100 showed that 3-monoCDF was the only strongly mutagenic congener (Matsumoto et al. 1988). This congener was mutagenic both with and without rat liver metabolic activation preparation, but metabolic activation increased mutagenic potency in both strains. 2-monoCDF was weakly mutagenic in strain TA98 with and without metabolic activation, and l- and 4-monoCDF showed no significant mutagenicity. Further testing with 3-monoCDF in *S. typhimurium* TA98 showed that this congener can be activated by both microsomal and other (cytosolic) enzymes from rat liver (Matsumoto and Ando 1991). In assays with the yeast *Saccharomyces cerevisiae* without exogenous metabolic activation, 2,3,7,8-tetraCDF did not induce forward mutations or inter- or intragenic recombinations (Fahrig et al. 1978). Although it appears that CDFs are generally not mutagenic in *in vitro* assays, due to their enzyme induction properties, they may potentiate the genotoxic activity of other compounds by activation to reactive intermediates. Genotoxic effects of other halogenated aromatic hydrocarbons are not known to be Ah receptor mediated.

2. HEALTH EFFECTS

Cancer. There is no conclusive evidence that CDFs are carcinogenic in humans. Human studies involving oral exposure include a retrospective mortality study of Yusho victims (Kuratsune et al. 1987) and an informal analysis of deaths associated with Yu-Cheng exposure (Hsu et al. 1985). Mortality from liver cancer increased significantly in the epidemiology study, but this cannot be definitely attributed to Yusho exposure, due to inconsistent occurrence among study prefectures. Approximately half of the observed Yu-Cheng deaths were attributed to hepatoma, cirrhosis, or unspecified liver diseases, but specific incidences and comparison values were not reported and background prevalences of hepatitis B, cirrhosis, and liver cancer in Taiwan are high.

No studies were located regarding cancer in animals after inhalation or oral exposure to CDFs. Dermal application of 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF for 20 weeks did not induce skin proliferative lesions in mice, but there was no post-treatment observation (Hebert et al. 1990). However, these CDFs as well as 2,3,7,8-tetraCDF promoted development of skin hyperproliferative nodules and squamous cell papillomas in mice following application of the tumor initiator MNNG (Hebert et al. 1990; Poland et al. 1982). Weekly subcutaneous injections of 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF for 4 or 20 weeks promoted development of enzyme-altered hepatic foci (putative preneoplastic lesions) and liver neoplasms in rats following promotion with N-nitrosodiethylamine (Nishizumi and Masuda 1986; Waern et al. 1991). Liver neoplastic nodules, hepatocellular carcinomas, and/or subcutaneous tumors were observed in some rats 104 weeks following subcutaneous injection of 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF as a single dose (61.5-69.6 μg/kg) or four weekly doses (38.1-40 μg/kg/week) (Nishizumi 1989). These findings are difficult to assess due to the small numbers of responders (one to two) and treated animals (five) in each group. Although the human studies are insufficient for evaluating possible carcinogenicity, the animal data suggest a potential for tumor promotion by CDFs.

Results of epidemiological studies and animal testing provide some evidence that 2,3,7,8-TCDD is carcinogenic (ATSDR 1994). The relevance of these findings to CDFs is unclear because it is not known if a common mechanism would be involved.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself 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 CDFs are discussed in Section 2.5.1.

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 CDFs are discussed in Section 2.5.2.

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 2.7, "Populations That Are Unusually Susceptible."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to CDFs

CDFs are pervasive environmental contaminants found in body tissues and fluids of the general population. Because they are lipophilic and have long half-lives, certain CDF congeners containing the 2,3,7,8-chlorine substitution pattern (particularly 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF) preferentially accumulate in lipid-rich tissues, especially adipose, and are present in whole blood, serum, or plasma and human milk. High amounts of CDFs are also found in the liver, and CDFs have been found at lower concentrations in all other tissues examined to date. Serum and adipose CDF levels are indicators of exposure that may provide an estimate of body burden because, as discussed in Section 2.3.2, some studies have reported that levels of CDFs and congener patterns are similar in serum, adipose, and other tissues when expressed on a fat weight basis (Ryan et al. 1985a; Schecter and Ryan 1989). However, concentrations of CDFs on a fat basis are higher in liver than in adipose (Beck et al. 1990; Thoma et al. 1990). A study of PCB exposure suggests that measurement in both serum and adipose may be more predictive of body burden than each parameter by itself, because concentration in serum varied with the concentration of lipids in serum (Brown and Lawton 1984). Measurements of CDFs in human milk have been used in general monitoring studies and provide some information on previous exposures, no reports were located that used these data to estimate body burden or environmental exposure levels. Quantitative exposure to CDFs can be estimated if the steady-state body burden and elimination half-lives of congeners are known. An elimination half-time from blood of ≈2-2.5 years was estimated for 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF in Yu-Cheng patients (Ryan et al. 1992b). Sampling was conducted over a g-year period starting 2 years after the incident. The same investigators (Ryan et al. 1992b) calculated a median elimination half-time of 10 years for the same congeners in Yusho patients. In this case, sampling was conducted over an 8-year period, but starting 14 years after the poisoning had occurred. Hair analysis may be a useful method for identifying recent exposure to CDFs in ambient air (Schramm et al. 1992).

Chloracne and changes in the Meibomian glands of the eyelid are effects clearly associated with significant exposure to CDFs based on outcomes of the Yusho and Yu-Cheng incidents. Although chloracne and lesions of the eyelid are biomarkers that are distinct and easily observed, they may not be the most sensitive indicators of human exposure. Additionally, these effects are not associated

specifically with CDFs, as they also can be induced by other chloroaromatic compounds (e.g., CDDs) that seem to act by a common Ah receptor-mediated mechanism (see Section 2.3.5). As discussed in Section 2.5.2, chloracne in Yu-Cheng victims was associated with an estimated body burden of 4.0 μg/kg/day of 2,3,4,7,8-pentaCDF equivalent (PEQ), or about 300 μg (PEQ) in an adult (Ryan et al. 1990).

2.5.2 Biomarkers Used to Characterize Effects Caused by CDFs

Body burden is a biomarker that may be useful for predicting effects of CDFs. A body burden associated with chloracne was calculated using total blood levels of CDFs in symptomatic Yu-Cheng victims (Ryan et al. 1990). An estimated mean uptake associated with chloracne was 4.0 μg/kg/day (PEQ), using a 1:l ratio of the two most toxic congeners (2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF) and a 5:l ratio in relative toxicity of these congeners. This is equivalent to ≈300 μg (PEQ) and 150 μg of 2,3,7,8-TCDD (TEQ) for an adult person. A comparison using 2,3,7,8-TCDD toxicity equivalent factors (see Section 2.4) showed that this estimate is >200 times higher than uptakes estimated from current average total levels of 2,3,7,8-substituted CDFs and CDDs in adipose in normal American and Canadian populations. Levels of CDFs in adipose could also be a useful biomarker for effects. Overall severity of clinical findings in six Yusho patients (four female, two male) was quantified using a numerical rating score and compared to subcutaneous adipose concentrations of 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, and 1,2,3,6,7,8-hexaCDF individually and in combination (Nakagawa and Takahashi 1991). For the four females, there was a strong correlation between the total score of clinical findings and adipose concentration of CDFs (r=0.9885 for total CDFs; r=0.8645-0.9804 for individual congeners). The correlation was weaker for the entire group of six patients (r=0.4833 for total CDFs; r=0.4416-0.5291 for individual congeners), the small number of males precluded additional analysis to determine if this was due to gender-related differences in response or the small group size.

Biochemical changes (e.g., increased serum levels of hepatic enzymes, disorders of lipid and carbohydrate metabolism, unbalanced porphyrin metabolism), and/or changes in liver size, ultrastructure, or histology can indicate effects induced by CDFs, but are not specific for these or other chemicals. Biochemical changes in the placenta of women exposed during the Yu-Cheng incident were evaluated for possible use as biomarkers (Lucier et al. 1987, 1990; Sunahara et al. 1987). Decreased placental epidermal growth factor receptor phosphorylation capacity was associated with

decreased birth weights, but this is likely to be a general effect of similarly structured chloroaromatic compounds. The caffeine breath test (CBT) appears to be a sensitive but nonspecific method for characterizing exposure and/or effects of CDFs and related chemicals (Lambert et al. 1992). In this test, [^{13}C-methyl] caffeine is ingested by subjects, and hepatic cytochrome P-450IA2-dependent caffeine 3-N-demethylase activity is monitored by determining the amount of caffeine exhaled as radiolabeled CO,. The CBT is not specific for CDFs since CDDs, PCBs, and other polyaromatic hydrocarbons also induce cytochrome P-450IA. In conclusion, no specific biomarkers of effects of CDFs were identified.

Additional information regarding biomarkers for effects can be found in OTA (1990) and CDC/ATSDR (1990). For a more detailed discussion of the health effects caused by CDFs, please see Section 2.2 of Chapter 2.

2.6 INTERACTIONS WITH OTHER SUBSTANCES

Since concurrent exposure to mixtures of CDFs, CDDs, and other chloroaromatics is common in the general environment, studies regarding interactions of CDFs with other substances have aimed almost exclusively at determining possible changes in the relative potency of individual congeners in the presence of other congeners or 2,3,7,8-TCDD. This is largely because in using the TEF approach to risk assessment of CDFs and CDDs (see Section 2.4), which assumes additivity of toxic responses, it is important to know whether or not interactions between congeners play a role in the final expression of a particular mixture's toxicity. Therefore, it is of vital importance to elucidate whether interactions occur and what is their nature, so that toxicity of mixtures is appropriately estimated, including mixtures associated with hazardous waste sites as well as the Yusho and Yu-Cheng incidents. The validity of the TEF approach for assessing mixtures of CDFs and CDDs has been investigated using both environmental (Eadon et al. 1986) and experimental mixtures (De Vito et al. 1993; Pluess et al. 1988b; Poiger et al. 1989) with varying results depending upon the end point assessed, as discussed below.

The reported guinea pig oral LD_{50} for a soot sample from the Binghamton State Office Building PCB transformer fire, which contained a mixture of CDDs, CDFs, and PCBs, was found equivalent to 58 ppm 2,3,7,8-TCDD (Eadon et al. 1986). The corresponding 2,3,7,8-TCDD equivalents of the soot sample ranged from 2 to 19 ppm based on subchronic toxicity data. Using data from the literature to

estimate the potency of the individual congeners in the soot, the investigators predicted that the soot contained ≈22 ppm 2,3,7,8-TCDD equivalents. This agreement between predicted and observed concentrations was considered good in light of the uncertainties associated with the analytical methods and toxicological data.

Additive effects, as well as usefulness of the TEF approach, have also been demonstrated in long-term feeding studies. Rats were fed a diet containing a mixture of 2,3,7,8-TCDD, 1,2,3,7,8-pentaCDF, and 1,2,3,6,7,8-hexaCDF for 13-weeks (Pluess et al. 1988b; Poiger et al. 1989). This mixture, which contained 1.5 ppb of 2,3,7,8-TCDD equivalents, induced toxic lesions in the thymus and liver of comparable severity to that caused by a dose of 2 ppb of 2,3,7,8-TCDD alone, indicating that the single compounds additively contribute to the toxicity of the mixture as predicted for whole animals.

A more recent study (De Vito et al. 1993) provides some evidence that the TEFs may be inadequate or need reevaluation, although only single response was evaluated. In this study, hepatic, skin, and lung EROD, and hepatic acetanilide-4-hydroxylase activities were determined in mice that were fed presumed equipotent doses (based on published TEFs) of 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 1,2,3,4,6,7,8,9-octa CDF, 2,3,7,8-TCDD, and several PCB congeners for 4 weeks. It was found that the doses did not produce equivalent induction of enzyme activity for many of these chemicals, indicating that the TEFs do not reliably predict potency at the enzyme level.

Administration of a mixture of 25 nmol 2,3,7,8-TCDD/kg and 200 nmol 2,3,7,8-tetraCDF/kg as a single subcutaneous injection to pregnant mice on days 9-11 of gestation resulted in an incidence of 80% cleft palate in the fetuses examined at day 18 (Krowke 1986). When each chemical, at the same concentrations, were administered separately, the incidence of cleft palate was 34% for 2,3,7,8-TCDD and 40% for 2,3,7,8-tetraCDF, suggesting an additive whole animal response for the mixture. Weber et al. (1985) had previously reported a more adequate analysis of similar results by showing dose additivity (by probit model analysis) between 2,3,7,8-tetraCDF and 2,3,7,8-TCDD regarding cleft palate incidence after oral administration to mice. Also, mixtures of 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF and of 2,3,4,7,8-pentaCDF and 2,3,4,5,3',4'-hexachlorobiphenyl had additive teratogenic effects (cleft palate and hydronephrosis) when administered orally to pregnant C57BL/6N mice (Birnbaum et al. 1987). Probit analysis of the data revealed parallel dose-response curves, which is compatible with a common and additive mechanism of action for whole animal data.

Co-treatment of DBA/2J mice with single intraperitoneal injections of 200 nmol 2,3,7,8-TCDD/kg and 50, 200, or 800 umol 1,3,6,8-tetraCDF/kg inhibited AHH induction 13%, 39%, and 18%, and EROD induction 17%, 34%, and 21%, respectively, compared to 2,3,7,8-TCDD alone (Bannister and Safe 1987). Therefore, the maximum partial antagonist activity of 1,3,6,8-tetraCDF was obtained at an agonist/antagonist ratio of 1,000/l. In C57BL/6J mice, co-treatment with 15 nmol 2,3,7,8-TCDD/kg and 10, 50, 100, 200, and 500 μmol 1,3,6,8-tetraCDF/kg significantly inhibited both AHH and EROD only at 200 μmol 1,3,6,8-tetraCDF/kg. In this case the maximum partial antagonist activity occurred at an agonist/antagonist ratio of 13,300/l. These results suggest that antagonist activity depends on the strain and the relative concentration ratios of agonist and antagonist.

Administration of single intraperitoneal doses of 1,3,6,8-tetraCDF and 2,3,7,8-TCDD to mice resulted in significant antagonism of the immunotoxic effects of 2,3,7,8-TCDD, as monitored by the splenic plaque-forming cell response to sheep red blood cells (Davis and Safe 1988). Similar results were reported for the combination of 1,3,6,8-tetraCDF and 2,3,4,7,8-pentaCDF. These results are consistent with previously published data showing that 1,3,6,8-tetraCDF has a high affinity for the cytosolic Ah receptor (Keys et al. 1986).

The viability of lymphocytes derived from mice fetal thymus organ culture was reduced by a combination of 3,4,3',4'-tetrachloroazoxybenzene and 2,3,7,8-tetraCDF in an additive manner (Hassoun 1987). While each compound induced a 25-50% reduction in cell viability, an equimolar combination reduced viability by 75%. The results suggest a common mechanism of action for the two chemicals, which is consistent with the fact that both substances bind to the Ah receptor.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to CDFs than will most persons exposed to the same level of CDFs in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons the elderly with declining organ function and the youngest of the population with immature

and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, "Populations With Potentially High Exposure."

No information was located on populations that may be unusually susceptible to CDFs. Strain differences in sensitivity to 2,3,7,8-TCDD toxicity are known to exist in mice and are associated with the Ah receptor (Poland and Glover 1980). Differences in human susceptibility to CDFs could be related to Ah receptor concentration, which has been shown to vary in lymphoid tissue among people (Lorenzen and Okey 1991).

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to CDFs. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as guide for treatment of exposures to CDFs. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

No specific information was located regarding the reduction of peak absorption of CDFs in humans. However, long-term medical surveillance (follow-up medical care) strategies have been published (Schecter 1985). After dermal exposure, the affected area should be flushed with plenty of water. In rats, simultaneous oral administration of 2,3,4,7,8-pentaCDF with either liquid paraffin or squalene (2,6,10,15,19,23-hexamethyltetracosane) greatly reduced gastrointestinal absorption of the CDF (Oguri et al. 1987). The relevance of this approach to the treatment of exposed humans is unknown.

2.8.2 Reducing Body Burden

As indicated in Section 2.3, high concentrations of CDF congeners can be retained in the fatty tissues and liver of exposed humans for long periods of time. Retention time is strongly related to the chlorine substitution pattern, and some congeners, particularly those with the 2,3,4,7,8-substitution pattern, may have elimination half-lives from <l year to several years (Schecter and Ryan 1989).

2. HEALTH EFFECTS

Since stored CDFs are constantly being redistributed among fatty tissues in the body in accordance with a dynamic equilibrium process among all tissues, it is reasonable to assume that congeners can exert toxic effects in susceptible tissues and organs while retained. One report that examined this issue suggests that fasting may be an effective therapy for reducing signs and symptoms of intoxication with aromatic halogenated hydrocarbons (Imamura and Tung 1984). In this study, 16 individuals who had ingested rice oil contaminated with PCBs and CDFs (Yu-Cheng patients) were maintained on a liquid diet for 7 or 10 days approximately 26 or 35 months after being poisoned. Several months after the fasting period, all the patients showed improvements of signs and symptoms of intoxication. The authors suggested that fasting may stimulate mobilization of CDFs (and PCBs) from adipose tissue to the liver where these chemicals are then metabolized, which would facilitate excretion and reduce body burden. The findings of this 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. Furthermore, body burden was not monitored. This therapy may not be recommended for pregnant women since, in this case, mobilization of CDFs from adipose tissue into the circulation may translate into increased fetal exposure since transplacental transfer can occur.

In experimental animals, administration of activated charcoal beads, paraffin oil, or squalene after ingestion of 2,3,4,7,8-pentaCDF accelerated (2- to 4-fold) fecal elimination of the compound, mainly by preventing reabsorption from the gastrointestinal tract (Kamimura et al. 1988, 1991; Oguri et al. 1987; Yoshimura et al. 1986). Promotion of fecal excretion of CDFs by cholestryamine, a hypercholesterolemia therapeutic agent used for treatment of poisoning by chlorinated organic agricultural chemicals, was inconclusive in a clinical trial with six Yusho patients in 1989 (Iida et al. 1991; Murai et al. 1991). In this study, fecal excretion of 2,3,7,8-tetraCDF, 2,3,4,7,8-pentaCDF, combined 1,2,3,4,7,8- and 1,2,3,6,7,8-hexaCDFs, 1,2,3,4,6,7,8-heptaCDF, and octaCDF, as well as PCBs, was evaluated throughout the treatment period in which 4 g cholestryamine was ingested three times daily for 6 months.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

There are no known methods for interfering with the mechanism of action of CDFs. Although the mechanism of action of CDFs is not completely understood, experimental evidence accumulated in recent years indicates that CDFs exert toxic actions by a process involving several steps (Safe 1990a).

This process begins with the binding of CDF congeners to the Ah receptor in the cytoplasm, and this complex leads ultimately to enhancement of the CYPlAl gene expression (see Section 2.3.5). It appears, therefore, that interfering with the initial step, binding to the receptor, or with any of the subsequent steps, would possibly prevent the expression of toxic effects. However, at this time, this concept is purely speculative, mainly because the Ah receptor and its properties, as well as its physiological role, have not been sufficiently characterized.

2.9 ADEQUACY OF THE DATABASE

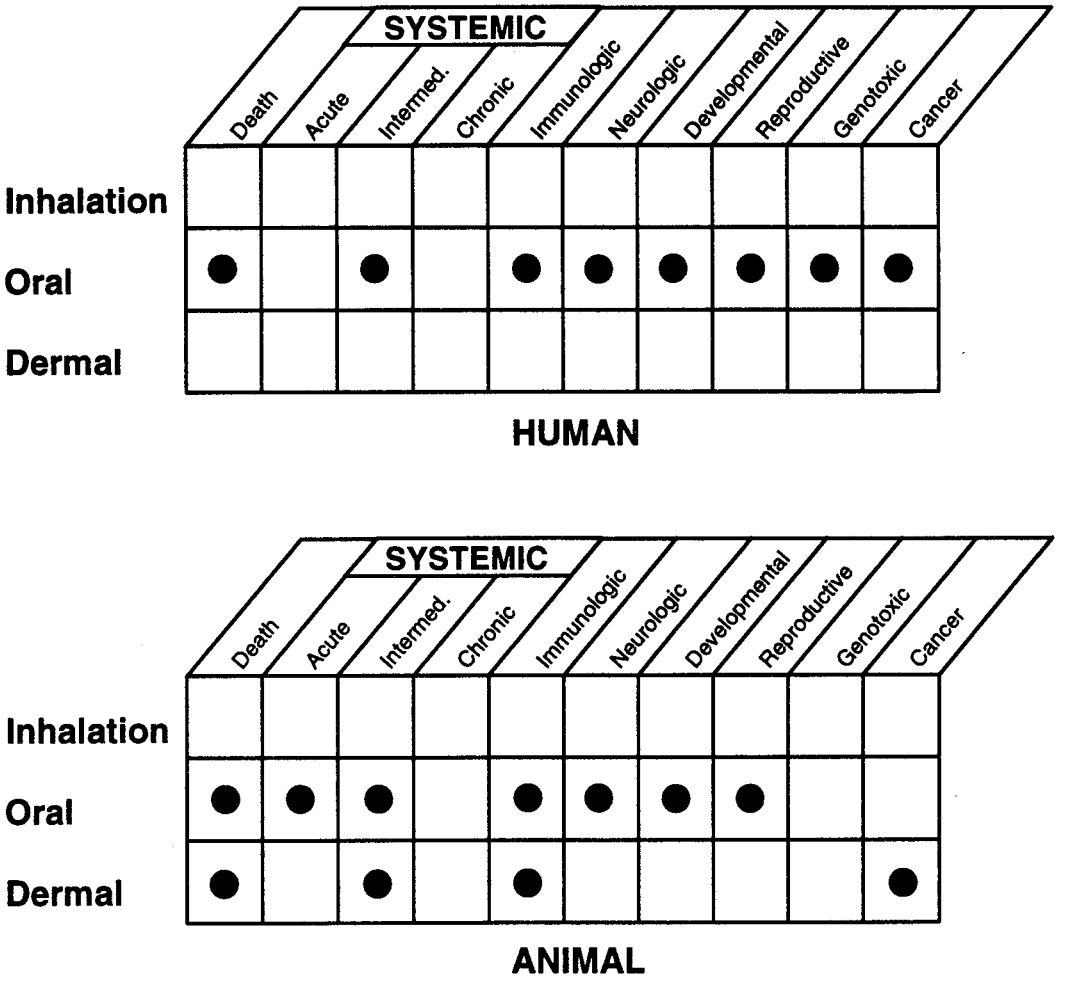
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of CDFs is available. Where adequate information is not available,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

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.

2.9.1 Existing Information on Health Effects of CDFs

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to CDFs are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of CDFs. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as “data needs.” 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.

FIGURE 2-2. Existing Information on Health Effects of Chlorinated Dibenzofurans



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2. HEALTH EFFECTS

As seen in Figure 2-2, information is available regarding death and systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects in humans. Essentially all of the information that pertains to likely effects of CDFs in humans is from the Yusho and Yu-Cheng rice oil poisoning incidents that involved intermediate duration oral exposure to contaminated PCBs. There is strong evidence that CDFs are the main (but not sole) causal agent in the health effects of the Yusho and Yu-Cheng victims. Limited information on effects in humans is available from the Binghamton State Office Building PCB fire incident that involved acute duration exposure to contaminated soot, probably by both dermal and inhalation routes. These studies are not summarized in Figure 2-2 because, as discussed in the introduction to Section 2.4, health effects cannot be attributed specifically to CDFs or any of the other components of the soot due to mixed chemical exposure, possible interactions between CDFs, PCBs, and other components of the contaminated rice oils, lack of confirmed doses, and other confounding factors. Since food is the major source of human exposure in the general population, the oral route is the most likely usual exposure route.

Oral and dermal studies in animals provide data on death, systemic effects resulting from acute- and intermediate-duration exposure, and immunologic, neurologic, developmental, reproductive, and carcinogenic effects. No data were located regarding effects in animals due to inhalation exposure to CDFs.

2.9.2 Identification of Data Needs

Most of the existing information on health effects of CDFs in animals has been obtained in tests using congeners fully substituted in the lateral (2,3,7,8) ring positions, particularly 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF. Studies of 2,3,7,8-tetraCDF were generally performed due to concern for high toxicity based on knowledge of 2,3,7,8-TCDD and other CDDs. Additional testing has shown, however, that CDFs with substitutions in positions 4 and 6 as well as 2,3,7,8 lateral substitutions, particularly 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF, are also relevant to health effects due to resistance to metabolism and preferential retention of these congeners. As discussed in Section 2.4, the EPA is using the TEF scheme as an alternative interim approach for hazard evaluation of CDFs and CDDs. Since only minimal toxicological data are available for most congeners, 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 (e.g., receptor binding affinity,

induction of oxidative enzymes, immunosuppression) 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.

CDFs and the structurally related and more extensively studied CDDs are a concern to ATSDR because of the potential of these chemicals to harm health at relatively low doses. As discussed in Section 2.4, many of the toxic effects of CDDs and CDFs 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 CDFKDD mixture probably results from the added contribution of both classes of chemicals. Because of this and other issues, including relevant studies of CDDs that are not yet completed, the complex issue of appropriate methodology for quantitatively assessing health risks of CDFs and CDDs is currently being evaluated by ATSDR. Additional information on toxic interactions between CDFs and CDDs, as well as PCBs, would facilitate health risk assessment of CDFs.

Acute-Duration Exposure. Essentially all of the information pertaining to health effects of CDFs in humans is from the Yusho and Yu-Cheng rice oil poisoning incidents. No definite information is available on human health effects of acute oral exposure to CDFs because exposure during these incidents predominately involved intermediate-duration exposure. It is possible that more detailed evaluation of the data on these poisoning incidents could provide insight on possible acute health effects. Information on humans exposed to PCB fires, particularly PCB mixtures not containing chlorinated benzenes (which can form CDDs), could possibly help characterize health effects of CDFs following acute dermal and/or inhalation exposure. Health effects associated with the Binghamton State Office Building electrical transformer fire cannot be attributed solely to CDFs or any of the other components of the soot due to the mixture of chemicals, which included chlorinated benzenes and CDDs, and other confounding factors, as discussed in the Introduction to Section 2.4.

Relatively little information is available on systemic effects of acute duration oral exposure to CDFs in animals. Several effects have been observed, including histopathologic and possible functional changes in the kidneys and gastrointestinal tract and evidence of wasting and anemia (Brewster et al. 1988; Moore et al. 1979). Many of these effects occurred at lethal or other high doses, although effects in the guinea pig, which is the most sensitive species tested in acute oral studies, are relatively well characterized. Since acute toxicity of CDFs may depend more on total dose, rather than frequency of dosing (i.e., after a critical body burden or tissue concentration is reached) (Luster et al.

1979a, 1979b; Moore et al. 1979), and is characteristically delayed in expression, some information from intermediate duration oral studies is relevant to acute exposure. Additional oral studies, however, could provide more suitable information on dose-response relationships at low levels, interspecies and interstrain differences in susceptibility, and effects at doses below the lowest currently known to cause adverse effects (i.e., developmental toxicity) following acute exposure. Data on effects in animals following acute dermal or inhalation exposure to CDFs are not available, although mobilization of CDFs from adipose tissue to target organs is likely to be similar, regardless of the route of exposure. Acute dermal studies are relevant because skin is a route of concern for exposure at or near hazardous waste sites, particularly due to possibilities for brief contact. Acute inhalation studies are unlikely to be relevant, due to the low potential for inhalation exposure in the vicinity of hazardous waste sites and ambient air.

Intermediate-Duration Exposure. Most of the existing toxicity information for CDFs is available from intermediate duration studies of orally-exposed humans following Yusho and Yu-Cheng poisoning and animals. Dermal and ocular effects; mild anemia; mild and transient hepatic alterations, including increased serum levels of triglycerides and liver enzymes and related ultrastructural changes; and bronchitis and other respiratory effects secondary to infection, were most consistently observed in the exposed humans (Kuratsune 1989; Rogan 1989). Although some estimates of doses associated with some effects of Yusho and Yu-Cheng exposure are available, these probably do not reflect the most sensitive toxic end points, as indicated by studies in rats, guinea pigs, and monkeys (Luster et al. 1979a, 1979b; McNulty et al. 1981; Pluess et al. 1988a, 1988b; Poiger et al. 1989). Some systemic effects of intermediate duration oral CDF exposure in animals are consistent with the effects observed in humans, but the animal studies better characterize progression of certain effects (e.g., liver toxicity) and have identified other systemic effects (e.g., wasting syndrome, stomach mucosal lesions) (McNulty et al. 1981; Moore et al. 1979; Oishi et al. 1978; Pluess et al. 1988a; Poiger et al. 1989). Hepatic effects in rats were used as a basis for an intermediate-duration oral MRL. Because of limitations in the database, it is unclear whether different species should be used for studying effects on different target organs. Additional animal studies could help identify NOAELs and characterize other aspects of dose-response for many of the effects, particularly in monkeys, which appear to be more sensitive than guinea pigs and other species based on observations in small numbers of animals (McNulty et al. 1991). These studies could also evaluate effects of oral dosages lower than those currently known to cause adverse effects (i.e., immunotoxicity) in intermediate duration studies, The only information available on systemic toxicity of intermediate duration dermal exposure is from a study in mice, which

found effects in the stomach and liver and on body weight (Hebert et al. 1990). Although these data are suggestive of similar effects by both dermal and oral routes, additional dermal studies could corroborate this and provide information on the sensitivity of other species, and are relevant because the skin is a route of concern for exposure at or near hazardous waste sites. No data were located regarding effects in animals after intermediate-duration inhalation exposure, but inhalation is a minor route of concern for humans.

Chronic-Duration Exposure and Cancer. No information is available on effects in humans or animals following chronic exposure to CDFs by any route. A retrospective mortality study of Yusho victims and an informal survey of Yu-Cheng deaths provides inconclusive evidence of liver cancer (Hsu et al. 1985; Kuratsune et al. 1987). Follow-up and/or more detailed analysis of deaths following Yusho and Yu-Cheng exposure could help ascertain the potential for oral carcinogenicity of CDFs. An intermediate duration study in mice showed no skin neoplastic activity following dermal application of 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF alone, although these congeners as well as 2,3,7,8-tetraCDF promoted development of mouse skin neoplasms (Hebert et al. 1990; Poland et al. 1982). These congeners also promoted development of liver tumors in rats following subcutaneous injection, providing further evidence of tumor promotion by CDFs. Results of a 2-year carcinogenicity study in which 2,3,4,7,8-pentaCDF or 1,2,3,4,7,8-hexaCDF were administered to rats by 1 single or 4 weekly subcutaneous injections are inconclusive due to small numbers of tested animals (Nishizumi 1989). Chronic exposure studies in animals could help elucidate the potential for oral and dermal carcinogenicity of CDFs in the absence of tumor initiators, and provide information on noncancer effect levels. Chronic oral studies should provide information relevant to dermal exposure, because toxicokinetic data suggest that the potential for systemic toxic and carcinogenic effects is likely to be qualitatively similar across routes. Also, chronic low-dose studies in animals would mimic the steady state of lifetime exposure in humans.

Genotoxicity. Limited information is available regarding genotoxic effects of CDFs in humans. Examination of lymphocytes of Yu-Cheng individuals revealed an increased frequency of sister chromatid exchanges. This effect could be attributed to PCBs that were found in the serum of these subjects at a concentration level 1,000 times higher than CDFs (Lundgren et al. 1988), because genotoxic effects of halogenated aromatic hydrocarbons are not known to be Ah receptor-mediated. Only 2,3,7,8-tetraCDF has been tested for genotoxicity in eukaryotic organisms (*S. cerevisiae* yeast) (Fahrig et al. 1978), and only monoCDFs, octaCDF, and 2,3,7,8-tetraCDF have been tested in

prokaryotes (*S. typhimurium* bacteria) (Matsumoto and Ando 1991; Matsumoto et al. 1988; Schoeny 1982). The results of these studies showed that 2,3,7,8-CDF was not mutagenic in *S. cerevisiae* and that CDFs were generally not mutagenic in various strains of *S. typhimurium,* with only 2- and 3-monoCDF inducing some activity. Additional studies with other congeners, in both eukaryotic and prokaryotic organisms *in vitro,* including bacteria, yeast, and rodent and human cells in culture, would provide valuable information regarding structure-activity relationships. Also, cytogenic analysis of human populations exposed to CDFs in occupational settings, or by consumption of food contaminated with CDFs would provide an opportunity to assess the genotoxic potential of these compounds in humans.

Reproductive Toxicity. Irregular menstrual cycles, abnormal basal body temperature patterns, and decreased urinary excretion of estrogens and pregnanediol were observed in female Yu-Cheng patients (Kusuda 1971). Although possibly suggestive of corpus luteum insufficiency and retarded follicular maturation, studies of fertility, fecundity, and rates of spontaneous abortion in Yu-Cheng and/or Yusho would provide more definite information on reproductive toxicity of CDFs. Some intermediate duration oral studies showed no histological alterations in the ovaries, uterus, or testes of rats treated with various CDFs (Pluess et al. 1988a, 1988b; Poiger et al. 1989), although there is some evidence from other oral studies (intermediate duration in rats and acute duration in guinea pigs) that the testes are a target (Moore et al. 1979; Oishi et al. 1978). Although pathological examinations performed as part of 90-day oral toxicity studies would be useful for identifying and corroborating susceptibility of the reproductive system and determining sensitive species, studies assessing effects of CDFs on reproductive function in males and females would be more informative. Such studies would enable the NOAEL region for reproductive effects to be better defined and provide assurance that MRLs are sufficiently protective. No information is available on reproductive effects of CDFs in animals or humans following dermal or inhalation exposure, but limited available toxicokinetic data suggest that the potential for reproductive toxicity is likely to be qualitatively similar across routes (Birnbaum et al. 1980; Brewster et al. 1989).

Developmental Toxicity. Various toxic effects have been observed in children born to mothers exposed during the Yusho and Yu-Cheng incidents, including dermal lesions, decreased birth weights, neurobehavioral deficits, and some perinatal deaths (Furatsu et al. 1971; Gladen et al. 1990; Hsu et al. 1985; Lan et al. 1987; Rogan et al. 1988; Taki et al. 1969; Yamaguchi et al. 1971; Yu et al. 1991). Although no exposure-related congenital malformations have been reported in these children, oral

studies in mice and rats have documented induction of hydronephrosis and/or cleft palate by 2,3,7,8-substituted tetra-, penta-, and hexaCDF congeners (Birnbaum et al. 1987a; Couture et al. 1989; Masden and Larsen 1989; Weber et al. 1984, 1985). Tissues other than kidney and palate were examined only in the rat studies, which provide some evidence indicating that rats are more susceptible to CDFs than mice and that neonatal thymic toxicity is a more sensitive developmental end point than fetal mortality or cleft palate in rats (Couture et al. 1989; Masden and Larsen 1989). Additional studies could verify that thymic toxicity is the most sensitive end point and the rat is the most sensitive species for developmental effects. Immunological evaluations of offspring would be valuable to determine the importance of thymic changes, and neurobehavioral evaluations in monkey offspring would be particularly relevant, due to the deficits observed in children of Yu-Cheng mothers. Since nursing can significantly contribute to offspring body burden and CDFs are retained in adipose long after external exposure has been discontinued, follow-up evaluations of sensitive developmental end points is desirable.

Immunotoxicity. Clinical observations of increased susceptibility to respiratory and dermal infections and various changes in immune parameters in Yusho and Yu-Cheng victims provide limited information on immunological effects of CDFs in humans (Chang et al. 1981, 1982a, 1982b; Kuratsune 1989; Lu and Wu 1985; Nakanishi et al. 1985; Rogan 1989; Shigematsu et al. 1971). Acute and intermediate duration oral exposure to CDFs induces decreased organ weight and atrophy in the thymus and to a lesser extent spleen in rodents and monkeys (Brewster et al. 1988; Luster et al. 1978a, 1979b; McNulty et al. 1981; Moore et al. 1979; Pluess et al. 1988a; Poiger et al. 1989). The induction of thymic toxicity at doses as low or lower than those know to cause other adverse effects in acute- and intermediate-duration studies indicates that the immune system may be one of the most sensitive targets for CDFs and provide a basis for an acute oral MRL. There is suggestive evidence of CDF-induced impaired functional immune response in guinea pigs (Luster et al. 1979a, 1979b), but an immunocompetence test in mice was inconclusive (Oishi and Hiraga 1980). Additional studies would be necessary to determine if the immune system is a critical target of CDFs. Decreased thymus and spleen weights with atrophy also occurred in mice dermally treated with CDFs in an intermediate duration study, indicating that immunological effects of CDFs are unlikely to be route specific (Hebert et al. 1990). No studies were located regarding developmental effects in humans or animals after inhalation exposure to CDFs.

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Neurotoxicity. Various neurological symptoms were common and there were some indications of reduced sensory and motor nerve conduction velocities in Yusho and Yu-Cheng victims (Chen et al. 1985a; Chia and Chu 1984, 1985; Kuratsune 1989; Rogan 1989). Furthermore, it should be mentioned that the developing nervous system appears to be a target for CDFs in children born to mothers with Yu-Cheng exposure (see Developmental Effects). Studies of rats and guinea pigs orally treated with CDFs for acute or intermediate durations provide no definite information on possible neurobehavioral toxicity, because nonspecific and/or insensitive end points (e.g., toxic signs, brain pathology) were evaluated (Brewster et al. 1988; Moore et al. 1979; Oishi et al. 1978). A battery of neurobehavioral studies, including neurohistology, would provide information on the susceptibility of animal species and could be used to corroborate the human data. Follow-up evaluations of the human populations already studied would help determine whether or not deficits observed in infants exposed *in utero* and through nursing progress into more severe alterations. Pertinent information is lacking on neurological effects of CDFs in humans and animals following dermal or inhalation exposure, but existing toxicokinetic data that do not suggest route-specific target organs.

Epidemiological and Human Dosimetry Studies. Studies of the Yusho and Yu-Cheng populations provide a wealth of information on health effects attributable to CDFs, and these populations are the best existing basis for assessing the effects of CDFs (Hsu et al. 1985; Kuratsune 1989; Kuratsune et al. 1987; Rogan 1989) in humans further. Additional studies could possibly provide information on dose-response for sensitive effects and discern which effects represent delayed and/or irreversible toxicity. Follow-up studies would also be useful for more adequately assessing risk of cancer. Municipal incineration workers (Schecter et al. 1991) and certain other worker populations (see Section 5.2.1) may be exposed to CDFs by inhalation and dermally, but co-exposure to CDDs and other chemicals is more of an issue than in the Yusho and Yu-Cheng incidents.

Biomarkers of Exposure and Effect

Exposure. Due to their lipophilicity, CDFs are stored in highest concentrations in adipose tissue and are frequently measured in blood and human milk, and have been found at lower concentrations in all other tissues examined to date. Several studies indicate that serum and adipose levels of CDFs are biomarkers of exposure feasible for estimating body burden or exposure (Brown and Lawton 1984; Ryan et al. 1985a; Schecter and Ryan 1989). Further studies on the predictive value of CDF levels in

human serum, adipose, and milk could provide valuable information that could lead to early detection of exposure.

Effect. A body burden association with chloracne has been calculated for CDFs using data from Yu-Cheng victims (Ryan et al. 1990). Additional studies could evaluate the feasibility of using body burden as a biomarker for predicting other effects of CDFs. Chloracne and many other effects of CDFs, however, are common to other chloroaromatics acting by the Ah receptor-mediated mechanism. There are no specific clinical or biochemical biomarkers of effects for CDFs, although some (e.g., changes in lipid and porphyrin metabolism) may be limited to chloroaromatics acting by the common mechanism. Further studies to identify specific biomarkers of effects of PCBs 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, oral, or dermal routes, but data from accidentally exposed individuals suggest that exposure by any of these routes, or a combination of them, may lead to considerable accumulation of CDFs in tissues (Chen et al. 1985b; Masuda et al. 1985; Schecter and Ryan 1989). The animal data indicate that CDFs (mostly tetra- and pentaCDFs) are efficiently absorbed by the oral route (Birnbaum et al. 1980; Brewster and Birnbaum 1987; Van den Berg et al. 1989). Inhalation absorption data are not available. Dermal absorption data were limited to one study in rats that showed relatively low absorption for two pentaCDFs, compared with oral rates (Brewster et al. 1989). No studies were located in which a range of doses of different CDF congeners were administered by the inhalation, oral, and dermal routes, and for various exposure periods.

As with absorption, distribution data in humans are limited to qualitative information derived from cases of accidental ingestion of food contaminated with CDFs (Chen et al. 1985b; Masuda et al. 1985), cases of occupational exposure through inhalation or dermal contact with CDFs (Schecter and Ryan 1989), and autopsy reports from the general population (Ryan et al. 1985a; Schecter et al. 1989a). These data suggest that CDFs distribute preferentially to tissues with high fat content regardless of the route of exposure. Data derived from oral and dermal administration of single CDF congeners to animals indicate that CDFs distribute first to the liver and are subsequently translocated to adipose tissue for storage (Brewster and Birnbaum 1987; Birnbaum et al. 1980; Brewster et al. 1989; Decad et al. 1981a). Studies regarding distribution through the placenta after inhalation and dermal exposures were not available.

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Data regarding biotransformation of CDFs in humans are limited to individuals who accidentally consumed food contaminated with CDFs (Chen et al. 1985b; Masuda et al. 1985). The use of human cell systems in culture might be considered a useful addition to whole animal studies for studying the metabolic fate of CDFs. The metabolism of some CDF congeners after acute oral administration to rats has been studied (Poiger and Pluess 1989). Although information regarding metabolism following inhalation or dermal exposure is lacking, there is no reason to believe that other pathways would operate after exposure by these routes.

Studies regarding urinary or fecal excretion of CDFs in humans were not located; however, elimination of CDFs through maternal milk is well documented (Van den Berg et al. 1986). Fecal excretion is the main route of elimination of CDFs in animals after acute oral exposure (Birnbaum et al. 1980; Brewster and Birnbaum 1987; Decad et al. 1981a; Weber and Birnbaum 1985). Excretion data following dermal exposure support the oral data, but the information is derived from a single study (Brewster et al. 1989). Although data regarding excretion after inhalation were not located, there is no reason to suspect different patterns of excretion.

Comparative Toxicokinetics. The existing evidence suggests that qualitative differences in the toxicokinetic disposition of CDFs exist among humans and among animal species. However, these differences appear to be highly dependent on the specific congener studied. In general, all species absorb CDFs efficiently and accumulate CDFs in tissues rich in fat. Once absorbed, CDFs distribute in a similar manner in all examined animal species (high initial concentration in blood, liver, and muscle, followed by gradual increase in CDF concentration in adipose tissue) (Bimbaum et al. 1980; Brewster and Birnbaum 1987; Decad et al. 1981a; Weber and Birnbaum 1985). Identification of metabolites in humans and rats suggests that both species share some common biochemical reactions (Chen et al. 1985b; Poiger and Pluess 1989). Experimental data in animals indicate that fecal elimination is the main route of excretion (Bimbaum et al. 1980; Brewster and Bimbaum 1987; Decad et al. 1981a; Weber and Bimbaum 1985), but no human information was located in the existing literature. Analysis of the excreta of humans accidentally exposed to CDFs or living near hazardous waste sites would provide information regarding biotransformation and elimination kinetics in humans. In addition similar target organs have been identified across animal species. Monkeys seem to be one of the most sensitive species tested. Although the toxicological data in humans are limited, adverse cutaneous and ocular (e.g., Meibomian gland) reactions documented in humans (Kuratsune 1989) are

also seen in monkeys (McNulty et al. 1981), suggesting that monkeys may represent a suitable animal model.

Methods for Reducing Toxic Effects. The mechanism by which CDFs enter the blood stream in humans is not known, consequently, there are no established methods for reducing absorption. In rats, however, simultaneous oral administration of paraffin oil or squalene reduced gastrointestinal absorption in an acute-duration study (Oguri et al. 1987). Identification of additional substances that could prevent or delay absorption and that do not represent a toxic risk per se would be valuable. There are no established methods for reducing body burden in humans, but a report indicated that fasting may be effective (Imamura and Tung 1984). Studies examining the effect of fasting in animals exposed to CDFs would provide useful information that can be used to better characterize the effectiveness of this approach. The mechanism of toxic action of CDFs is not completely understood and no methods exist to block the toxic response due to exposure to CDFs. A more complete characterization of the cytosolic receptor protein, to which CDFs are thought to bind, and understanding of physiological effects of receptor blockage would be useful for the possible identification of blockers of that reaction. There are no established methods for mitigation of health effects resulting from exposure to CDFs.

2.9.3 On-going Studies

Dr. S. Safe and his colleagues at the Texas A & M University are studying the antiestrogenic responses in rodents and human breast cancer cells in culture of a series of 1,3,6&substituted CDFs (FEDRIP 1992, 1993). The project involves characterization of the antiestrogenic response in human cells, determination of the mechanism of action of these chemicals, and determination of anti-tumorigenic effects of these compounds in nude athymic mice.

Dr. Safe and his group are also attempting to characterize the structure-activity relationship for higher chlorinated CDFs using a battery of Ah receptor-mediated *in vivo* assays. Furthermore, they also propose to validate the utility of *in vitro* assays for monoxygenase enzyme and cytochrome P-450 mRNA induction as methods for quantitatively assessing the toxic equivalents of complex mixtures. Additional studies conducted by Dr. Safe's group are focusing on characterizing some of the properties of the Ah receptor with newly synthesized radiolabeled CDFs.

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Dr. K. Randerath, also from Texas A & M University, and co-workers are investigating the mechanism of carcinogenesis of halogenated aromatic hydrocarbons by utilizing the highly sensitive 32P-postlabeling assay for detecting DNA adducts (FEDRIP 1992).

Dr. A. Poland and his research team, at the University of Wisconsin, propose to screen human lymphoblastoid cell lines for variants of the Ah receptor and determine the functional significance of these variants. Dr. Poland is also investigating the occurrence of the Ah receptor in invertebrates (FEDRIP 1992).

A group of investigators at SUNY, Albany, headed by Dr. D. Carpenter, are conducting an epidemiological study in a population adjacent to a Superfund-designated landfill contaminated with CDFs and PCBs (FEDRIP 1992). They will try to correlate contaminant levels in fish and wildlife consumed by pregnant and nursing mothers with levels in body fluids and breast milk, and with levels in urine and feces of infants. Studies in rats aim to assess developmental, neurological, and hepatic effects after pre- and postnatal exposure to CDFs. Dr. Carpenter is also studying the effects of CDF exposure on the invertebrate sea snail, *Aplysia.*

Dr. G. Lucier at the National Institute of Environmental Health Sciences (NIEHS) is examining placentas from humans exposed to CDFs in Taiwan and comparing biochemical changes such as enzyme induction in the placentas to those occurring in rats (FEDRIP 1992).

Dr. L. Birnbaum and colleagues at NIEHS are continuing studies designed to elucidate the absorption rates and disposition of CDFs, and the effects of age on these parameters, in experimental animals (FEDRIP 1993).

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Dibenzofuran is an organic compound that contains two benzene rings fused to a central furan ring. CDFs are a class of organic compounds in which one to eight chlorine atoms are attached to the benzene ring positions of a dibenzofuran structure. The general chemical structure for CDFs with the numbering system is as follows:

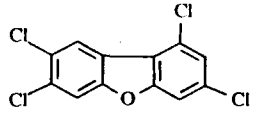
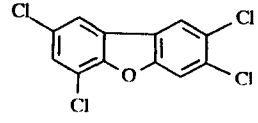
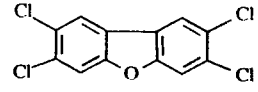
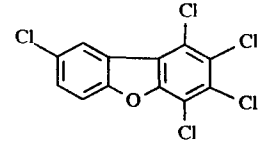
Based on the number of chlorine substituents (one to eight) on the benzene rings, there are eight homologues of CDFs (monochlorinated through octachlorinated). Each homologous group contains one or more isomers. There are 135 possible CDF isomers, including 4 monoCDFs, 16 diCDFs, 28 triCDFs, 38 tetraCDFs, 28 pentaCDFs, 16 hexaCDFs, 4 heptaCDFs, and one octaCDF. Each one of these compounds is called a congener. Because of molecular asymmetry, CDFs have 135 congeners, compared to 75 for CDDs.

The synonyms, chemical formulas, chemical structure, and identification numbers of selected CDFs are reported in Table 3-l. CDFs that are known or suspected to be most toxic (2,3,7,%substituted congeners) and other CDFs, for which health effects data are discussed in Section 2, have been selected for inclusion in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

CDFs have been synthesized in quantities <1 g. The methods needed to separate the isomeric compounds in a congener series make the isolation of an individual congener difficult. Therefore, data pertaining to the simplest physical and chemical properties of the individual congener are not generally available. The extremely low water solubilities and vapor pressures contribute to the difficulty in determining these and related physico-chemical properties (e.g., K_{OW} and Henry's law constant) of these compounds. In general, the melting point increases and the vapor pressures and water

TABLE 3-1. Chemical Identities of CDFs

Characteristic	1,3,7,8-TetraCDF	2,3,6,8-TetraCDF	2,3,7,8-TetraCDF	1,2,3,4,8-PentaCDF
Synonyms[a]	1,3,7,8-Tetrachlorodiphenylene oxide	2,3,6,8-Tetrachlorodiphenylene oxide	2,3,7,8-Tetrachlorodiphenylene oxide	1,2,3,4,8-Pentachlodiphenylene oxide
Registered trade names	No data	No data	No data	No data
Chemical formula	$C_{12}H_4Cl_4O$	$C_{12}H_4Cl_4O$	$C_{12}H_4Cl_4O$	$C_{12}H_3Cl_5O$
Chemical structure				
Identification numbers:				
CAS registry[b]	57117-35-8	57117-37-0	51207-31-9	67517-48-0
NIOSH RTECS	No data	No data	HP5295200[c]	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data
HSDB	No data	No data	4306	No data
NCI	No data	No data	C56611	No data

[a]Weast 1985
[b]EPA 1986
[c]NIOSH 1987

CAS = Chemical Abstracts Services; CDF = Chlorodibenzofuran; 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 3-1. Chemical Identities of CDFs *(continued)*

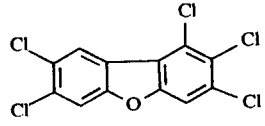
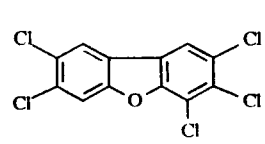
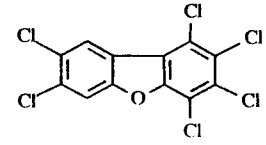
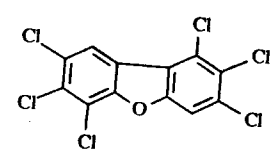
Characteristic	1,2,3,7,8-PentaCDF	2,3,4,7,8-PentaCDF	1,2,3,4,7,8-HexaCDF	1,2,3,6,7,8-HexaCDF
Synonyms[a]	1,2,3,7,8-Pentachlorodiphenylene oxide	2,3,4,7,8-Pentachlorodiphenylene oxide	1,2,3,4,7,8-Hexachlorodiphenylene oxide	1,2,3,6,7,8-Hexachlorodiphenylene oxide
Registered trade names	No data	No data	No data	No data
Chemical formula	$C_{12}H_3Cl_5O$	$C_{12}H_3Cl_5O$	$C_{12}H_2Cl_6O$	$C_{12}H_2Cl_6O$
Chemical structure				
Identification numbers:				
CAS registry[b]	57117-41-6	57117-31-4	70648-26-9	57117-44-9
NIOSH RTECS	No data	HP52955150[c]	No data	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data
HSDB	No data	No data	No data	No data
NCI	No data	No data	No data	No data

TABLE 3-1. Chemical Identities of CDFs *(continued)*

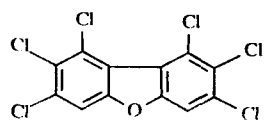
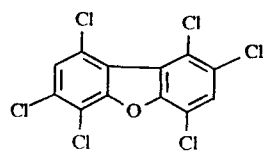
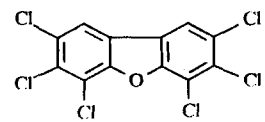
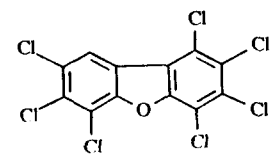
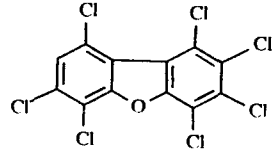
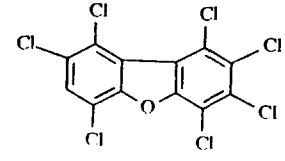
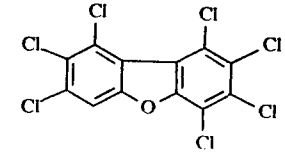
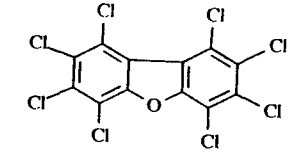
Characteristic	1,2,3,7,8,9-HexaCDF	1,2,4,6,7,9-HexaCDF	2,3,4,6,7,8-HexaCDF	1,2,3,4,6,7,8-HeptaCDF
Synonyms[a]	1,2,3,7,8,9-Hexachlorodiphenylene oxide	1,2,4,6,7,9-Hexachlorodiphenylene oxide	2,3,4,6,7,8-Hexachlorodiphenylene oxide	1,2,3,4,6,7,8-Heptachlorodiphenylene oxide
Registered trade names	No data	No data	No data	No data
Chemical formula	$C_{12}H_2Cl_6O$	$C_{12}H_2Cl_6O$	$C_{12}H_2Cl_6O$	$C_{12}HCl_7O$
Chemical structure				
Identification numbers:				
CAS registry[b]	72918-21-9	75627-02-0	60851-34-5	67562-39-4
NIOSH RTECS	No data	No data	No data	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data
HSDB	No data	No data	No data	No data
NCI	No data	No data	No data	No data

TABLE 3-1. Chemical Identities of CDFs *(continued)*

Characteristic	1,2,3,4,6,7,9-HeptaCDF	1,2,3,4,6,8,9-HeptaCDF	1,2,3,4,7,8,9-HeptaCDF	1,2,3,4,6,7,8,9-OctaCDF
Synonyms[a]	1,2,3,4,6,7,9-Heptachlorodiphenylene oxide	1,2,3,4,6,8,9-Heptachlorodiphenylene oxide	1,2,3,4,7,8,9-Heptachlorodiphenylene oxide	1,2,3,4,6,7,8,9-Octachlorodiphenylene oxide
Registered trade names	No data	No data	No data	No data
Chemical formula	$C_{12}HCl_7O$	$C_{12}HCl_7O$	$C_{12}HCl_7O$	$C_{12}Cl_8O$
Chemical structure				
Identification numbers:				
CAS registry[b]	70648-25-8	69698-58-4	55673-89-7	39001-02-0
NIOSH RTECS	No data	No data	No data	No data
EPA hazardous waste	No data	No data	No data	No data
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data	No data
HSDB	No data	No data	No data	No data
NCI	No data	No data	No data	No data

solubilities of the CDFs decrease as the number of chlorine substituents increases (see Table 3-2). These hydrophobic compounds are generally colorless solids and are soluble in nonpolar organic solvents (Gray et al. 1976). The CDFs are relatively stable towards acid and alkali attack, but they start to decompose at 700°C (see Section 4.4) (Van den Berg et al. 1985). The physical and chemical properties of CDFs are given in Table 3-2.

TABLE 3-2. Physical and Chemical Properties of CDFs

Property	1,3,7,8-TetraCDF	2,3,6,8-TetraCDF	2,3,7,8-TetraCDF	1,2,3,4,8-PentaCDF
Molecular weight	305.96	305.96	305.96	340.42
Color[a]	No data	Colorless[b]	Colorless	No data
Physical state[a]	No data	Solid[c]	Solid	No data
Melting point, °C[a]	No data	197-198	219-221	177-178
Boiling point	No data	No data	No data	No data
Density	No data	No data	No data	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water[d]	No data	No data	1.37×10^{-9} mol/L (0.42 µg/L)	No data
Organic solvent(s)[e]	Soluble in toluene	Soluble in toluene and chloroform	Soluble in toluene	Soluble in toluene
Partition coefficients:				
Log K_{ow}[f]	No data	No data	5.82[g]	6.79
Log K_{oc}[h]	No data	No data	5.61 (estimated)	No data
Vapor pressure, mm Hg[i] (25°C)	No data	No data	9.21×10^{-7}	No data
Henry's law constant[j] (atm-m^3/mol)[k]	1.48×10^{-5}	1.48×10^{-5}	1.48×10^{-5}	2.63×10^{-5}
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors				
Air[b] (at 20°C)	1 ppb = 12.719 µg/m^3	1 ppb = 12.719 µg/m^3	1 ppb = 12.719 µg/m^3	1 ppb = 14.151 µg/m^3
Water	1 ppb = 1 µg/L	1 ppb = 1 µg/L	1 ppb = 1 µg/L	1 ppb = 1 µg/L
Soil	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg	1 ppd = 1 µg/kg
Explosive limits	No data	No data	No data	No data

[a]Kuroki et al. 1984 unless otherwise stated
[b]The PCDFs are present predominantly in the particulate phase in ambient air (Hunt and Maisel 1990)
[c]Gray et al. 1976
[d]Friesen et al. 1990 unless otherwise stated
[e]Ryan et al. 1991 unless otherwise stated
[f]Sijm et al. 1989 unless otherwise stated; some of the values are for two isomers that could not be separated.
[g]Burkhard and Kuehl 1986
[h]EPA 1986
[i]Eitzer and Hites 1988
[j]Eitzer and Hites 1989; the values are for unseparated isomers of each homologous series
[k]Frank and Schrap 1990

CDF = chlorodibenzofuran

TABLE 3-2. Physical and Chemical Properties of CDFs *(continued)*

Property	1,2,3,7,8-PentaCDF	2,3,4,7,8-PentaCDF	1,2,3,4,7,8-HexaCDF	1,2,3,6,7,8-HexaCDF
Molecular weight	340.42	340.42	374.87	374.87
Color[a]	Colorless	No data	No data	No data
Physical state[a]	Solid	No data	No data	No data
Melting point, °C[a]	225-227	196-196.5	225.5-226.5	232-234
Boiling point	No data	No data	No data	No data
Density	No data	No data	No data	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water[d]	No data	6.92×10^{-10} mol/L (0.24 µg/L)	2.20×10^{-11} mol/L (0.008 µg/L)	4.72×10^{-11} mol/L (0.018 µg/L)
Organic solvent(s)[e]	Soluble in hexane[a] and toluene	Soluble in toluene	Soluble in toluene	Soluble in toluene
Partition coefficients:				
Log K_{ow}[f]	6.79	6.92	No data	No data
Log K_{oc}[h]	No data	No data	No data	No data
Vapor pressure, mm Hg[i] (25°C)	2.73×10^{-7}	1.63×10^{-7}	6.07×10^{-8}	6.07×10^{-8}
Henry's law constant (atm-m^3/mol)[j]	2.63×10^{-5}	2.63×10^{-5}	2.78×10^{-5}	2.78×10^{-5}
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors				
Air[b] (at 20°C)	1 ppb = 14.151 µg/m^3	1 ppb = 14.151 µg/m^3	1 ppb = 15.583 µg/m^3	1 ppb = 15.583 µg/m^3
Water	1 ppb = 1 µg/L	1 ppb = 1 µg/L	1 ppb = 1 µg/L	1 ppb = 1 µg/L
Soil	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg
Explosive limits	No data	No data	No data	No data

TABLE 3-2. Physical and Chemical Properties of CDFs *(continued)*

Property	1,2,3,7,8,9-HexaCDF	1,2,4,6,7,9-HexaCDF	2,3,4,6,7,8-HexaCDF	1,2,3,4,6,7,8-HeptaCDF
Molecular weight	374.87	374.87	374.87	409.31
Color[a]	No data	No data	No data	No data
Physical state[a]	No data	No data	No data	No data
Melting point, °C[a]	No data	180-181	239-240	236-237
Boiling point	No data	No data	No data	No data
Density	No data	No data	No data	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water[d]	No data	No data	No data	3.31×10^{-12} mol/L (0.014 µg/L)
Organic solvent(s)[e]	Soluble in toluene	Soluble in toluene	Soluble in toluene	Soluble in toluene
Partition coefficients:				
Log K_{ow}[f]	No data	No data	No data	7.92
Log K_{oc}[h]	No data	No data	No data	No data
Vapor pressure, mm Hg[i] (25°C)	3.74×10^{-8}	No data	3.74×10^{-8}	1.68×10^{-8}
Henry's law constant (atm-m^3/mol)[j]	2.78×10^{-5}	2.78×10^{-5}	2.78×10^{-5}	4.1×10^{-6}
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors				
Air[b] (at 20°C)	1 ppb = 15.583 µg/m^3	1 ppb = 15.583 µg/m^3	1 ppb = 15.583 µg/m^3	1 ppb = 17.015 µg/m^3
Water	1 ppb = 1 µg/L	1 ppb = 1 µg/L	1 ppb = 1 µg/L	1 ppb = 1 µg/L
Soil	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg
Explosive limits	No data	No data	No data	No data

TABLE 3-2. Physical and Chemical Properties of CDFs *(continued)*

Property	1,2,3,4,6,7,9-HeptaCDF	1,2,3,4,6,8,9-HeptaCDF	1,2,3,4,7,8,9-HeptaCDF	1,2,3,4,6,7,8,9-OctaCDF
Molecular weight	409.31	409.31	409.31	443.76
Color[a]	No data	No data	No data	No data
Physical state[a]	No data	No data	No data	No data
Melting point, °C[a]	No data	211-212	212-223	259[c]
Boiling point	No data	No data	No data	537[c]
Density	No data	No data	No data	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water[d]	No data	No data	No data	2.61×10^{-12} mol/L (0.0012 µg/L) (3.0 µg/L)[k]
Organic solvent(s)[e]	Soluble in toluene	Soluble in toluene	Soluble in toluene	Soluble in toluene
Partition coefficients:				
Log K_{ow}[f]	No data	No data	No data	8.20 (7.97)[i]
Log K_{oc}[h]	No data	No data	No data	8.57 (estimated)
Vapor pressure, mm Hg[i] (25°C)	No data	No data	9.79×10^{-9}	No data
Henry's law constant (atm-m^3/mol)[j]	4.1×10^{-6}	4.1×10^{-6}	4.1×10^{-6}	1.7×10^{-6}
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors				
Air[b] (at 20°C)	1 ppb = 17.015 µg/m^3	1 ppb = 17.015 µg/m^3	1 ppb = 17.015 µg/m^3	1 ppb = 18.447 µg/m^3
Water	1 ppb = 1 µg/L	1 ppb = 1 µg/L	1 ppb = 1 µg/L	1 ppb = 1 µg/L
Soil	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg	1 ppb = 1 µg/kg
Explosive limits	No data	No data	No data	No data

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

4.1 PRODUCTION

CDFs are not manufactured commercially in the United States or any other country except on a laboratory scale for use in chemical laboratories or for toxicological studies. These compounds are produced as undesired by-products during the manufacture of PCBs, polychlorinated phenols, and herbicides, such as Agent Orange. They are also formed during the pyrolysis of PCBs, polychlorinated diphenyl ethers, polychlorinated phenols, polychlorinated benzenes, and phenoxy herbicides. Municipal and industrial incinerators also produce CDFs. These compounds can also be produced from the photolysis of PCBs, polychlorinated diphenyl ethers, and polychlorinated benzenes (Van den Berg et al. 1985). Chlorine bleaching at paper and pulp mills can also result in CDF formation (Campin et al. 1991; Näf et al. 1992). Detailed information on the sources of CDFs are given in Chapter 5.

Several methods are available for the synthesis of CDFs; all yield mixtures of isomers (EPA 1986a; Gara et al. 1981). Two methods that have been used to synthesize a number of structure-specific CDFs are cyclization of diazotized chlorophenoxy-o-aniline and cyclization of chlorinated diphenylethers, promoted by palladium(I1) acetate (Gara et al. 1981; Gray 1976; Humppi 1986; Kuroki et al. 1984; Norstrom 1979). In the first process, chlorophenates and chloronitrobenzene react to form nitrochlorodiphenyl ethers. The later compounds are reduced to aminochlorodiphenyl ethers, diazotized, and cyclized with isoamyl nitrite to form the CDFs. In the second method, chlorinated diphenyl ethers are produced by refluxing chlorinated diphenyl iodonium salt with chlorophenolate. The chlorinated diphenyl ethers are cyclized with palladium acetate in the presence of acetic acid and methane sulfonic acid (Kuroki et al. 1984).

Another method that has been used to synthesize 22 high purity CDF isomers is the cyclization of o-hydroxy polychlorinated biphenyls by refluxing with dimethyl sulfoxide and potassium hydroxide (Safe and Safe 1984). The o-hydroxyl PCBs are produced either by a diazo coupling of chlorinated anisidines and symmetrical chlorinated benzenes or by diazo coupling of chlorinated anilines with chlorinated anisoles.

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

The pyrolysis of PCBs, commercial chlorobenzenes, and chlorinated diphenyl ethers yields CDF mixtures. Although the pyrolysis method produces mixtures of isomeric CDFs, it has been used frequently to prepare qualitative CDF standards, because it is fast and safe (Buser and Rappe 1979; EPA 1986a; Grace et al. 1989). Similarly, qualitative standard mixtures of CDFs have also been produced by the ultraviolet and gamma irradiation of octachlorodibenzofuran (Buser 1976).

Since SARA Section 313 does not require that releases of CDFs be reported, there are no data on these compounds in the 1989 Toxics Release Inventory (TRI) (TRI89 1992).

4.2 IMPORT/EXPORT

No data were located on the import or export of CDFs.

4.3 USE

There is no commercial use of CDFs other than small amounts used in chemical and biochemical laboratories.

4.4 DISPOSAL

Several methods for disposing CDFs have been proposed; some of these have been put into field use to decontaminate wastes containing CDFs. The most commonly used methods for disposal or decontamination of CDF-containing wastes are photolysis, incineration, chemical destruction, microbial degradation, and landfilling. Each of these methods has limitations, but some may be preferable to others. The common methods for CDF waste disposal/decontamination are discussed below.

In the photolytic process, CDDs/CDFs are destroyed by dechlorination of the compounds by ultraviolet light most efficiently in the presence of hydrogen donors. The most commonly used hydrogen donor is isopropyl alcohol (des Rosiers 1983). TCDD-containing Seveso soil was decontaminated by ultraviolet treatment of the soil in the presence of olive oil emulsion as a hydrogen donor. A total reduction in excess of 60% was observed after 48 hours of irradiation. The decontamination efficiency of CDFs by ultraviolet radiation was reported to be 90% after 48 hours irradiation of the walls and ceiling of a building contaminated during a PCB fire (Borwitzky and Schramm 1991). When CDFs

were extracted from a contaminated soil in hexane and irradiated with ultraviolet light in the presence of a hydrogen donating solvent (propanol), the decontamination efficiency reached 99.9% in 4 hours (Drechsler 1986). The destruction efficiencies of CDFs by liquid phase photolysis are faster than CDDs (Muto and Takizawa 1991). The advantage of photolytic destruction is that it poses only a small risk to workers. The notable disadvantages of the photolysis process are that it is time consuming (when a large area is involved or solvent extraction is performed) and may not be universally applicable to other contaminants (Borwitzky and Schramm 1991).

Incineration is a preferred method for disposing of CDF-containing wastes. In this process, the waste is burned in a stationary or rotary kiln incinerator at temperatures between 900 and 1,000°C and a minimum residence time of 1.8 seconds; however, the destruction of particle bound CDFs may require higher temperatures and longer retention times. Higher temperatures can be attained by adding a secondary combustion chamber to a rotary kiln incinerator. Land-based and at-sea incineration facilities are available. Investigators have postulated the following combustion criteria for land-based incineration of CDF wastes: a 2-second dwell time at 1,200°C or 15second dwell time at 1,600°C, a combustion efficiency in excess of 99.99%, and a scrubber system to control flue gas emission (Almemark et al. 1991; des Rosiers 1983). EPA considers CDFs Principal Organic Hazardous Constituents (POHCs) and requires them to be incinerated, in order to achieve a destruction and removal efficiency of 99.99% (EPA 1990b).

Some of the chemical methods available for the destruction of CDFs include alkaline dehydrochlorination; reduction with hydrogen in the presence of a palladium or platinum catalyst at 100°C; catalytic oxidation with ruthenium tetroxide, chlorolysis in the presence of chlorine gas at 600°C and a pressure of 170 atm; or micellar catalysis with either benzalkonium dichloroiodide or cetylpyridinium dichloroiodide. Disadvantages of these methods are generation of unwanted byproducts requiring high temperatures or pressures and, in some cases, cost. The preferable chemical method is dehydrochlorination in a mixture of alkaline polyethylene glycol and inorganic peroxide at a temperature <l00°C (des Rosiers 1983; Drechsler 1986; Hagenmaier et al. 1987; Tiernan et al. 1989). A chemical method employing precipitation by the addition of alum or lime at a concentration of 9,000 mg/L removed >98% of CDDs/CDFs from bleach plant filtrates and combined treated mill effluents from pulp and paper industries (Barton et al. 1990). However, the sludge from this process contains the CDDs/CDFs and requires proper disposal. The destruction of CDFs in aqueous solution

at a pH of 10 and temperature of 50°C by ozone was reported to be >90% in 4 hours (Palauschek and Scholz 1987).

Decontamination of CDF-containing wastes by a biodegradation method has also been attempted. *Phanerochuete chrysosporium,* a white rot fungus, which degraded TCDD in laboratory experiments (des Rosiers 1986), may be suitable for biodegrading CDFs. However, no successful biotreatment method exists that can satisfactorily decontaminate CDF wastes.

In the past, land disposal of waste materials contaminated with CDDs and CDFs was considered an option under strict technical conditions. Some of these conditions included use of soil with low water permeability, the use of synthetic membrane liners to cover the soil, compatibility with the hydrogeology of the site, maintenance of a leachate monitoring program, and acquisition of waivers from the appropriate EPA or state agency (des Rosiers 1983). However, land disposal of certain CDF wastes is presently prohibited. The Toxic Substances Control Act (TSCA) regulates the use, disposal, and distribution in commerce of process waste water treatment sludges intended for land application that are derived from pulp and paper industry employing chlorination processes (EPA 1991).

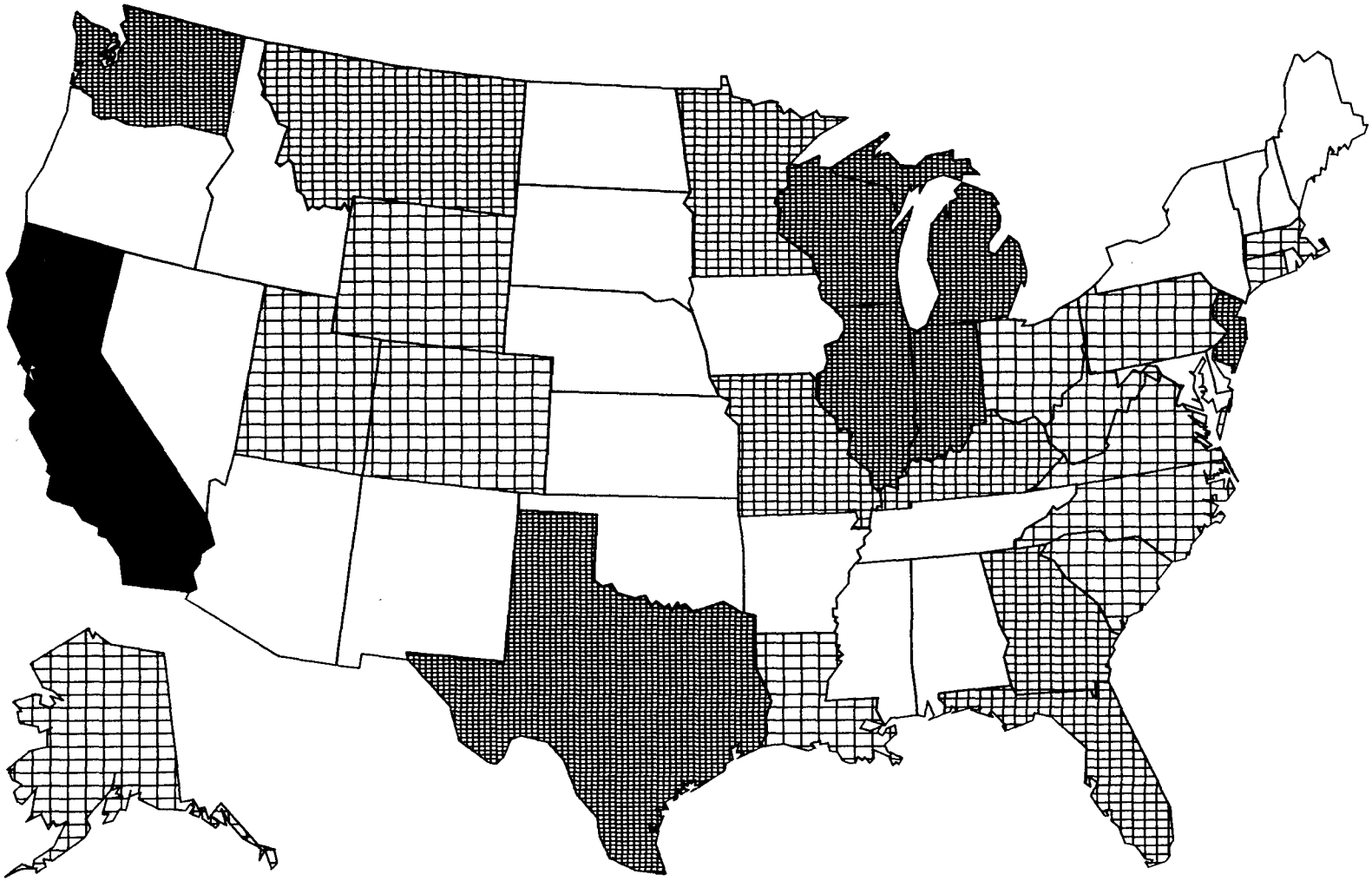
5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Low levels of CDFs occur as contaminants in certain chemical products and during combustion of certain precursors of CDFs. The processes that are responsible for the production of CDFs in the environment form a mixture of congeners. In addition, many of the combustion processes that produce CDFs also produce structurally similar compounds, such as CDDs and chlorinated dibenzothiophenes (CDTs). Due to the similarity in their physicochemical properties, including low water solubility, high lipid solubility, low vapor pressure, and multiple chlorine substitution, these compounds are generally found together in environmental samples. Therefore, environmental exposures to CDFs occur not only from a mixture of CDFs, but also from CDDs, CDTs, and other structurally similar compounds and other structurally similar compounds present as cocontaminants. To simplify the assessment of human health risk of a mixture of CDDs and CDFs, EPA has recommended the TEF approach (see Section 2.4).

The sources of CDFs in the environment are combustion processes mainly involving municipal and industrial incineration; combustion of fossil fuels by power plants, home heating and fireplaces; automobile exhaust; medical waste incineration; yard waste cornposting; accidental fires or malfunction of PCB-filled transformers and capacitors; improper disposal of chlorinated chemical wastes; use of certain chemical products (e.g., chlorinated phenols); certain high temperature industrial processes, such as copper smelting, electrical arc furnaces in steel mills, and production of metallic magnesium and refined nickel; chlorine bleaching of pulp and paper; and photochemical processes involving certain products, such as chlorinated diphenyl ethers. Some of these sources emit CDFs in the air, while others discharge CDFs as effluents in surface water. The source of these compounds in soil is disposal of chemical wastes containing CDFs as contaminants. The deposition of atmospheric CDFs is also an important source of these compounds in surface water and soil. EPA has identified 1,300 NPL sites. CDFs have been found in at least 57 of the sites evaluated for their presence (HAZDAT 1991). However, the number of sites evaluated for the presence of CDFs is not known. The frequency of these sites within the United States can be seen in Figure 5-1.

FIGURE 5-1. FREQUENCY OF NPL SITES WITH CDFs CONTAMINATION *



*Derived from HAZDAT 1991

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In the atmosphere, the higher chlorinated CDFs are present predominantly in the particulate phase, but tetra- and pentaCDFs may be present in the vapor phase as well. Due to higher atmospheric temperatures, the concentrations of CDFs in the vapor phase increase during summer. The most important chemical process in determining the fate of CDFs in air is the reaction with hydroxyl radicals. The lifetime of CDFs due to this process is >l0 days, and increases with higher chlorinated CDFs, which allows these compounds to be transported long distances in air. Wet and dry deposition. of atmospheric CDFs may also be important for the removal of these compounds from air. CDFs will be present in water mainly in the particulate-sorbed phase. Significant loss of CDFs in water, either due to chemical reactions including photochemical reactions or biodegradation processes, has not been observed. CDFs in water partition into the particulate phase and settle into the sediment. Sediment is the ultimate sink of atmospheric and aquatic CDFs. CDFs bioconcentrate in aquatic organisms, but the bioconcentration factor is lower than the predicted value based on the K_{OW} value, due to the ability of fish to partially metabolize these compounds. CDFs are very persistent in soils. They also strongly adsorb to soil; consequently, very little vertical movement of these compounds has been observed in soil.

The concentrations of CDFs in air usually exist in the following order: rural < suburban < urban < industrial/ auto tunnel. The concentrations of total tetra-, penta-, hexa-, hepta-, and octaCDF in ambient urban/suburban air vary, ranging from 0.13 to 7.34, 0.09 to 5.10, <0.09 to 12.55, 0.08 to 12.71, and 0.13 to 3.78 pg/m^3, respectively. CDFs were detected in 1 of 20 water supplies in New York State. The only congener groups detected in this water were tetraCDF at a concentration 2.6 ppq (pg/L) and octaCDF at a concentration of 0.8 ppq. The levels of CDFs in contaminated water, such as effluents from a kraft pulp mill, can be three orders of magnitude higher than the levels in drinking water. The levels of CDF in various foods consumed in Germany, Japan, Canada, and the United States are also available, and the level in individual food products is on the order of pg/kg.

The general population is exposed to CDFs by inhaling air, ingesting food, soil, and water, and from consumer products (e.g., paper towels, tampons). The estimated total intake of CDDs/CDFs from all these sources in a Canadian background population is 2.4 pg toxic equivalent to 2,3,7,8-TCDD/kg body weight/day. The intake from food constitutes ≈96% of the total toxic intake. Fish and fish products, milk and milk products, and meat and meat products each constitute ≈30% of CDF food intake in Germany. Because of this CDF body burden in background populations and the tendency of

CDFs to bioconcentrate in fat, the levels of CDFs in adipose tissue, human milk, and the lipid portion of blood in both background and exposed populations have been determined.

Workers in saw mills, in the textile industry, in the leather industry, in the pulp and paper industries, in certain chemical manufacturing and in PCB user industries (repairing transformers or capacitors, using casting waxes containing PCBs) may be exposed to a higher level of CDFs than the background population. Among the general population, groups who consume high amounts of fatty fish, people who are exposed to accidental fires involving PCBs, and nursing babies are potentially exposed to higher levels of CDFs. People living near incinerators may be exposed to elevated levels of CDFs. The levels will depend on the nature of the waste being incinerated. People who live adjacent to uncontrolled landfill sites containing high concentration of CDFs may also be exposed to higher concentrations of CDFs. Diverse studies indicate that the levels of CDFs in the adipose tissue of exposed populations are higher than those in unexposed or background populations.

5.2 RELEASES TO THE ENVIRONMENT

CDFs in the environment are primarily of anthropogenic origin (Czuczwa and Hites 1986a, 1986b). Trace amounts of CDFs may come from sources, such as forest fires, which may not be anthropogenic in origin (Bumb et al. 1980). The levels of CDDs and CDFs in archived soil samples collected from the same semi-rural area in southeast England between 1846 and 1986 were found to increase around the turn of the century (A.D. 1900) (Kjeller et al. 1991; Rappe 1991). Higher levels of CDFs are found in human tissue (Ligon et al. 1989; Rappe 1991) and river silt (Schecter 1991) samples collected from industrial countries than those from less industrial countries or from ancient civilization. These results suggest that most CDFs found at present are of anthropogenic origin.

The primary sources of environmental release of CDFs can be divided into the following five categories: thermal reactions, chemical reactions, photochemical reactions, enzymatic reactions, and hazardous waste sites.

Thermal Reactions

Combustion Processes. The combustion processes can be divided into two categories, large systems and small systems. Municipal waste incineration (Bonafanti et al. 1990; Brna and Kilgore 1990; des

Rosiers 1987; Hutzinger and Fiedler 1989; Siebert et al. 1987; Tiernan et al. 1985; Tong and Karasek 1986), incineration of industrial and hazardous wastes (des Rosiers 1987; Muto et al. 1991), and power plants with fossil fuels (des Rosiers 1987; Hutzinger and Fiedler 1989) are examples of large systems. Small combustion systems include home heating and fireplaces (Clement et al. 1985; Safe 1990a), household waste incineration (Harrad et al. 1991a), automobile exhaust (Ballschmiter et al, 1986; Marklund et al. 1987), and medical waste incineration (des Rosiers 1987; Glasser et al. 1991; Lindner et al. 1990). Incineration of industrial and hazardous wastes that produce CDFs include wastes containing PCBs (Choudhury and Hutzinger 1982; Hutzinger and Fiedler 1989; Sedman and Esparza 1991), polychlorinated diphenyl ethers (Choudhury and Hutzinger 1982), 2,4,5-trichlorophenol esters (Choudhury and Hutzinger 1982) and chlorinated benzenes (Choudhury and Hutzinger 1982; Öberg and Bergstrom 1987), chlorophenols (Narang et al. 1991; Gberg and Bergstrom 1987), waste oil (Taucher et al. 1992), biosludge from paper and pulp mills (des Rosiers 1987; Mantykoski et al. 1989; Someshwar et al. 1990) polyvinyl chloride (Christmann et al. 1989a), municipal sewage sludge (Clement et al. 1987; des Rosiers 1987), and chlorinated fluorenones and 9,10-anthraquinones (Boenke and Ballschmiter 1989). The typical concentrations of total tetraCDFs, pentaCDFs, hexaCDFs, heptaCDFs, and octaCDF in municipal waste incineration fly ash are 79.5, 120.3, 116.3, 108.2, and 42.9 ppb, respectively (Safe 1990a). The corresponding CDF concentrations in soot from home heating oil are 28.9, 16.6, 6.2, 1.8, and 0.3 ppb and in soot from coal/wood burning for home heating are 50.8, 30.0, 11.7, 3.2, and 0.5 ppb. The concentrations of 2,3,7,8-tetraCDF congener in municipal fly ash, soot from heating oil and soot from coal/wood burning are 2.5, 1.1, and 1.9 ppb, respectively. The combined bottom and fly ash from five state-of-the-art mass-bum municipal waste combustors, with a variety of pollution control equipment, were analyzed for CDFs. The concentrations of CDFs (rig/kg or ppt) in ash samples were determined to be: 2,3,7,8-tetraCDF, 176-626; 1,2,3,7,8-pentaCDF, 52-194; 2,3,4,7,8-pentaCDF, 43-171; 1,2,3,4,7,8-hexaCDF, 74-654; 1,2,3,6,7,8-hexaCDF, 131-660; 1,2,3,7,8,9-hexaCDF, 36-479; 2,3,4,6,7,8-hexaCDF, 5-124; 1,2,3,4,6,7,8-heptaCDF, 139-1,842; 1,2,3,4,7,8,9-heptaCDF, 8-l 19 (EPA 1990).

Three mechanisms have been postulated for the formation of CDFs in combustion processes. They are: (1) CDFs are already present in trace amounts within the fuel and are not destroyed during combustion; (2) CDFs are formed during combustion from precursors (e.g., PCBs, PCPs), which are present in the fuel; and (3) *de novo* synthesis from nonchlorinated organic substance and chlorine-containing molecules (Hutzinger and Fiedler 1989). Details about the mechanisms of CDF formation in combustion processes are available (Choudhury and Hutzinger 1982; Hutzinger and Fiedler 1989;

Jay and Stieglitz 1991; Stieglitz et al. 1989). Other investigators have studied the control technologies available for the reduction of CDF emissions from municipal waste combustors (Brna and Kilgore 1990; Jordan 1987; Takeshita and Akimoto 1989). A significant reduction of CDF-concentrations in the flue gas from municipal and industrial waste incinerators and fossil fuel-fired power stations can be achieved either by the addition of a mixture of anhydrous calcium hydrate and coke to the flue gas or by treating the flue gas with titanium dioxide catalyst in the presence of ammonia (Hagenmaier et al. 1991).

Accidental Fires or Malfunction of PCB-filled Transformers and Capacitors. Some of the major fires/ malfunctions involving PCB transformers and capacitors in the United States include a transformer fire inside the state office building in Binghamton, New York, in 1981; a transformer fire inside an office building in Boston, Massachusetts, in 1982; a transformer fire adjacent to a high-rise building in San Francisco, California, in 1983; a transformer fire inside an office building in Chicago, Illinois, in 1983; and a capacitor fire inside an office building in Columbus, Ohio, in 1984 (des Rosiers and Lee 1986; Hryhorczuk et al. 1986; Stephens 1986; Tiernan et al. 1985). CDFs were detected in air, soot, or wipe samples from all these fire incidents. However, it was determined that in the absence of fire, CDF levels do not appear to increase in PCB fluids in electrical equipment from normal usage (des Rosiers and Lee 1986). The concentrations of total tetraCDFs, pentaCDFs, hexaCDFs, heptaCDFs, and octaCDF in air samples from different locations of a building following a transformer fire in San Francisco ranged from not detected to 53.9, not detected to 11 .0, not detected to 1.3, not detected to 3.7, and not detected to 165.0 pg/m^3, respectively (Stephens 1986). A maximum concentration of 2,3,7,8-tetraCDF inside the building air was 18.5 pg/m^3 (Stephens 1986). The concentration range of 2,3,7,8-tetraCDF in soot samples from other transformer/capacitor fires in the United States was 3-1,000 μg/g (des Rosiers and Lee 1986). Other reports of international fires/accidents involving PCBs that lead to the formation of CDFs and the mechanism of CDF formation from PCBs are also available (Erickson 1989; Hutzinger et al. 1985).

Certain Industrial Processes. Certain high-temperature industrial processes like copper smelting, electrical arc furnaces in steel mills, production of metallic magnesium and refined nickel emit CDFs in the atmosphere and process waste waters at concentrations higher than those found in emissions from municipal incineration and automobile exhausts (Oehme et al. 1989; Rappe 1987). It has been theorized that contamination/coating with polyvinyl chloride or polychlorinated paraffins are the precursors for the formation of CDFs in copper smelting and steel production from scrap metals

(Rappe 1987). It has been speculated, in the case of magnesium and nickel production, that heavy metals in the presence of chlorine catalyze the formation of CDFs. But the precursors of CDFs have not been identified (Oehme et al. 1989).

Cigarette Smoke. Both mainstream and sidestream cigarette smoke contain CDFs. The smoke contained 2,3,7,8-substituted congeners of CDFs, and the concentrations of total CDFs in mainstream and sidestream smoke of one common commercial brand of Swedish cigarette were 720 and 1,670 pg per 20 cigarettes, respectively (Lofroth and Zeburh 1992). The concentrations of CDFs in the smoke is likely dependent on the manner in which a cigarette is smoked and the tobacco chlorine concentration (Lofroth and Zeburh 1992).

Chemical Reactions

Certain Chemical Products. CDFs occur as contaminants in a number of chemical products, such as chlorinated phenols, PCBs, phenoxy herbicides, chlorodiphenyl ether herbicides, hexachlorobenzene, tetrachlorobenzoquinones, and certain dyes. These chemical products containing CDFs may be released into the environment during their manufacture, use, or disposal.

The level of CDFs in commercial chlorinated phenols from different countries are given in Table 5-l. The difference in the levels of isomeric congeners is due to different degrees of chlorination and different methods of synthesis. The major CDF isomers identified were 1,2,4,6,8-penta-, 1,2,3,4,6,8-hexa-, 1,2,4,6,7,8-hexa-, 1,2,4,6,8,9-hexa-, 1,2,3,4,6,7,8-hepta-, and 1,2,3,4,6,8,9-heptaCDF (Rappe and Buser 198 1). Commercial pentachlorophenol and sodium pentachlorophenate, used extensively for the preservation of wood, contained trace amounts of CDFs (Hagenmaier and Brunner 1987). These substances have the potential to migrate away or volatilize from wood surfaces and contaminate indoor air. The concentrations of CDFs in indoor ambient air of a kindergarten building in West Germany using PCP-treated wood were as follows: non-2,3,7,8-tetraCDF, 0.27 pg/m^3; 1,2,3,7,8-pentaCDF, 0.1 pg/m^3; non-2,3,7,8-pentaCDFs, 3.51 pg/m^3; 1,2,3,4,7,8-hexaCDF, 0.37 pg/m^3; 1,2,3,6,7,8-hexaCDF, 0.60 pg/m^3; 1,2,3,7,8,9-hexaCDF, 0.16 pg/m^3; non-2,3,7,8-hexaCDFs, 12.3 pg/m^3; 1.2,3,4,6,7,8-heptaCDF, 10.7 pg/m^3; 1,2,3,4,7,8,9-heptaCDF, 0.38 pg/m^3; non-2,3,7,8-heptaCDFs, 12.2 pg/m^3; and octaCDF, 6.0 pg/m^3 (Mukerjee et al. 1989). Therefore, use of certain commercial products can be a source of CDFs in air.

TABLE 5-1. Levels of CDFs in Commercial Chlorinated Phenols (µg/g)[a]

	CDFs						Σ CDDs
	Tetra	Penta	Hexa	Hepta	Octa	Σ CDFs	
2,4,6-Trichlorophenol, Sweden	1.5	17.5	36	4.8	—	60	<3
2,4,6-Trichlorophenol, USA	1.4	2.3	0.7	<0.02	—	4.6	0.3
2,3,4,6-Tetrachlorophenol, Finland	0.5	10	70	70	10	160	12
Pentachlorophenol, USA	0.9	4	32	120	130	280	1,000
Pentachlorophenol, USA	—	—	30	80	80	190	2,625
Pentachlorophenol, USA	≤0.4	40	90	400	260	790	1,900
Pentachlorophenol, Germany	—	—	0.03	0.8	1.3	2.1	6.8

[a]Rappe and Buser 1981

CDDs = chlorinated dibenzo-*p*-dioxins; CDFs = chlorinated dibenzofurans

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From the analysis of air particulates and sediment, it was concluded that the likely source of CDFs in a western Lake Ontario site was a pentachlorophenol production facility (Czuczwa and Hites 1986).

Commercial Aroclors, Clophen A-60, and Phenoclor DP-6 were analyzed for CDF concentrations (Bowes et al. 1975a). The concentrations of 2,3,7,8-tetraCDF and 2,3,4,7,8-pentaCDF in two Aroclors and two Japanese Kanechlors were also determined (Bowes et al. 1975). The concentrations of CDFs in a number of commercial PCB samples are given in Table 5-2. The CDF isomers identified in commercial PCBs are 2,3,7,8-tetra-, 2,3,6,7-tetra-, 2,3,6,8-tetra-, 2,3,4,7,8-penta-, 1,2,3,7,8-penta-, 1,2,4,7,8-penta-, 1,2,3,4,7,8-hexa-, 1,2,4,6,7,8-tetra-, 1,2,4,6,8,9-hexa-, 1,2,3,4,5,7,8-hepta-, and 1,2,3,4,6,8,9-heptaCDF (Rappe and Buser 1981).

Phenoxy herbicides generally contain higher concentrations of CDDs than CDFs. Therefore, more effort has been spent to determine the levels of CDDs in these samples. Two samples of European 2,4,5-trichlorophenoxyacetic acid contained non-2,3,7,8-tetraCDF. One sample of Agent Orange (a 50:50 mixture of n-butyl esters of 2,4-D and 2,4,5-trichlorophenoxyacetic acid) contained CDFs; they were one tri-, four tetra-, and one pentaCDF at a total concentration of 0.7 μg/g (EPA 1986a). It did not contain any 2,3,7,8-tetraCDF. Compost from municipal yard waste was also found to contain CDFs, possibly due to the presence of a PCP-based biocide (Harrad et al. 1991b).

CDFs have been detected as contaminants in commercial samples of diphenyl ether herbicides. Concentrations of tetraCDFs, pentaCDFs, and hexaCDFs in these samples were as high as 0.4, 1.0, and 0.2 ppb, respectively (Yamagishi et al. 1981).

Three early commercial hexachlorobenzene preparations were analyzed for CDFs. One sample contained a heptaCDF; all three samples contained octaCDF at concentrations ranging from 0.35 to 58.3 ppm (Villaneueva et al. 1974).

Samples of eight commercially available tetrachlorobenzoquinones (chloranils) from four different producers were analyzed for CDFs. OctaCDF was found in seven of eight samples at a maximum concentration of 6.02 ppm, while 1,2,3,4,6,7,8-heptaCDF was found in four of eight samples at a maximum concentration of 27 ppb. 1,2,3,4,7,8-HexaCDFs, pentaCDFs, and tetraCDFs were also found in some of the samples (Christmann et al. 1989b).

TABLE 5-2. Levels of CDFs in Commercial PCBs (µg/g)

Sample	Tri-	Tetra-	Penta	Tetra	Hexa	Total
Aroclor 1248, 1969[a]	—	0.5	1.2	0.3	—	2.0
Aroclor 1254, 1969[a]	—	0.1	0.2	1.4	—	1.7
Aroclor 1254, 1970[a]	—	0.2	0.4	0.9	—	1.5
Aroclor 1254[b]	0.10	0.25	0.70	0.81	—	1.9
Aroclor 1254 (lot KK 602)[b]	—	0.05	0.10	0.02	—	0.2
Aroclor 1260, 1969[a]	—	0.1	0.4	0.5	—	1.0
Aroclor 1260 (lot AK 3)[a]	—	0.2	0.3	0.3	—	0.8
Aroclor 1260[b]	0.06	0.30	1.0	1.10	1.35	3.8
Aroclor 1016, 1972[a]	—	<0.001	<0.001	<0.001	—	—
Clophen A 60[a]	—	1.4	5.0	2.2	—	8.4
Clophen T 64[b]	0.10	0.30	1.73	2.45	0.82	5.4
Phenoclor DP-6[a]	—	0.7	10.0	2.9	—	13.6

[a]Bower et al. 1975a
[b]Rappe and Buser 1981

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CDFs are also formed during the bleaching process for the manufacture of pulp and paper (Campin et al. 1991; Kitunen and Salinoja-Salonen 1989; Näf et al. 1992). Low levels (ppt) of 2,3,7,8-substituted congeners of tetra-, penta-, hexa-, and heptaCDF have been identified in the pulp, finished paper boards, effluents, and sludges from paper mills and 2,3,7,8-TCDF has been found in fish downstream of plant effluent.

The chloroalkali process utilizing graphite electrode is used for the production of chlorine produces CDFs. Total CDF levels as high as 650 ng/g (ppb) of sludge have been detected in sludge samples from graphite electrodes of a chloroalkali plant (Rappe et al. 1991b). The levels of tetra-, penta-, and hexaCDFs in the sludge were found to be approximately the same.

A number of commercial dyes were analyzed for CDFs. These samples contained tetra-, penta-, hexa-, hepta-, and octaCDFs at the ppb level (Heindl and Hutzinger 1989; Remmers et al. 1992; Williams et al. 1992).

Photochemical Reactions

Certain Photochemical Processes Involving Commercial Products. 1,3,7,9-TetraCDF was formed from the photolysis of 2,2',4,4',6,6'-hexachlorobiphenyl in hexane-methanol solution (Safe et al. 1977). The rate of photolysis was markedly higher in oxygen-degassed solutions than in oxygen-saturated solutions, indicating a triplet state as a possible intermediate for the photolysis process (Safe et al. 1977). Photolysis of chlorinated diphenyl ethers at around 300 nm in a degassed methanol solution also produced mono-, di-, tri-, and tetraCDFs (Choudhury et al. 1977). Photodegradation of polychlorobenzenes can also be a source of CDFs (EPA 1986a). In addition, dechlorination of higher CDFs can be a source of lower chlorinated CDFs (see Section 5.3.2). The relevance of laboratory photolysis to environmental sources of CDFs is unknown.

Enzymatic Reactions. CDFs are formed by enzyme-catalyzed oxidations of 2,4-di-, 2,4,5-tri-, 2,3,4,6-tetra-, 2,3,5,6-tetra-, and penta-chlorophenol (ijberg and Rappe 1992; Svenson et al. 1989a, 1989b). The implication of these investigations is that CDFs may be biogenically formed from wastes containing these chlorophenols, but the significance of the process in contributing to the release of CDFs in the environment has not been assessed.

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Hazardous Waste Sites. The improper disposal of CDF-containing wastes in landfill sites will primarily contaminate soils (see Section 5.2.3), but the air may also be contaminated by wind blown dusts.

5.2.1 Air

CDFs are released to air from combustion processes, accidental fires or malfunction of PCB-filled transformers and capacitors, improper disposal of chlorinated chemical wastes, certain chemical products, certain industrial processes, and certain photochemical processes involving commercial products. Toxic Release Inventory (TRI) data are not available for CDFs since releases of these compounds are not required to be reported (TRI90 1992).

5.2.2 Water

CDFs enter water as a result of deposition after these compounds have been emitted to the atmosphere from combustion sources. The concentrations and congener patterns of CDFs found in the sediment of three lakes and in the atmosphere led the authors to conclude that atmospheric deposition is the primary source of these compounds in lakes (Czuczwa and Hites 1986).

CDFs will enter surface water as a result of the discharge of CDF contaminated waste water, which is generated during the manufacture of chemicals containing CDFs contaminants. 2,3,7,8-TetraCDF has been detected at concentrations ≤4.5 ppb in sediment from estuaries adjacent to an industrial site in which chlorinated phenols were produced (Bopp et al. 1991). The typical waste waters from magnesium and refined nickel production are also examples of such CDF contamination (Oehme et al. 1989). Chemical manufacturing waste contaminated with CDFs that has been improperly disposed can leach from landfills into groundwater. CDF contaminated soil sites have been found in Butte, Montana, and Kent, Washington (Tiernan et al. 1989a).

Another important source of CDFs in surface water is the discharge of effluents from pulp and paper mills that use the bleached kraft process. The concentrations of 2,3,7,8-tetraCDF in the treated effluents from five bleached kraft pulp and paper mills in the United States ranged from not detected (0.007 ppt) to 2.2 ppt with a mean value of 0.54 ppt, but the waste water sludges contained 2,3,7,8-tetraCDF at a mean concentration of 0.37 ppb (Amendola et al. 1989). The effluent from a

kraft pulp mill from Jackfish Bay, Lake Superior, contained tetraCDFs in concentrations ranging from 0.3 to 1.3 ng/L (9.3-1.3 ppt) (Sherman et al. 1990). Uncontrolled landfills can be sources of CDFs for adjacent surface waters (Clement et al. 1989c).

Chlorination of water has been shown to be a source of trace amounts (ppq level [i.e., pg/L level]) of CDFs. Apparently, impurities in the water may form CDFs on chlorination.

5.2.3 Soil

The main sources of CDFs in soil are atmospheric deposition from combustion and manufacturing processes and disposal of CDF-contaminated wastes. Several instances of CDF environmental contamination from improper disposal of hazardous chemical wastes have been associated with the manufacture or use of certain chlorinated organic compounds, and wastes from certain bleaching processes (Someshwar et al. 1990; Tieman et al. 1989). Soil samples around two wood-preserving facilities in Finland that used chlorophenols contained several congeners of CDFs (Kitunen et al. 1987). The concentrations of octaCDF, 1,2,3,4,6,8,9-heptaCDF, 1,2,3,4,6,7,8-heptaCDF, 1,2,4,6,8,9-hexaCDF, 1,2,4,6,7,8-hexaCDF, and 1,2,3,4,6,8-hexaCDF in the top soil from one of these facilities were 210, 840, 1,400, 440, 340, and 550 μg/kg, respectively. In the other facility, the concentrations of CDFs decreased with soil depth, then increased at a depth of 60-80 cm, and tended to decrease at depths ≥100 cm of soil (Kitunen et al. 1987). Soil contaminated with CDFs from PCP-containing wood preserving waste sites has been found in Butte, Montana, and Kent, Washington, in the United States (Tiernan et al. 1989), and in Finland (Kitunen et al. 1987). Land disposal of treated waste water sludge from magnesium and nickel production is another example of CDF soil contamination (Oehme et al. 1989). An important source of CDFs in soil is the discharge of waste water sludge from bleached kraft pulp and paper mills. The sludge from paper mills is known to contain CDFs (Amendola et al. 1989; Sherman et al. 1990; Someshwar et al. 1990). The presence of CDFs in the soil of Superfund sites also indicates that disposal of contaminated waste (e.g., waste from certain combustion processes, chemical wastes) is an important source of CDFs in soil. TetraCDFs, pentaCDFs, hexaCDFs, heptaCDFs, and octaCDF have been detected in soil samples from Superfund sites (HAZDAT 1991).

5.3 ENVIRONMENTAL FATE

5. POTENTIAL FOR HUMAN EXPOSURE

5.3.1 Transport and Partitioning

CDFs are present in the atmosphere both in the vapor and particulate phase (Hites 1990). The ratio of the vapor to particulate phase CDFs in air increases with increasing temperature. The ratio in Bloomington, Indiana was as high as 2 during the warm summer months and <0.5 in the winter. However, it should be recognized that the distribution of CDFs between the vapor and particulate phase will depend on the amount and nature of the particulate matter in the atmosphere, as well as the temperature (Hites 1990). The vapor to particle ratio is also different for the different congeners. In the air, a higher proportion of tetraCDF congeners is present in the vapor phase, whereas heptaCDF and octaCDF congeners are found predominantly in the particulate phase (Hites 1990). The transport of atmospheric CDFs to soil and water occurs by dry and wet deposition. Dry deposition refers to the simple gravitational settling of particles and the removal of vapor phase compounds onto surface materials, such as water and vegetation by impaction. Wet deposition refers to the removal of the atmospheric compounds by rain, fog, or snow.

The overall determined average dry to wet deposition ratio for atmospheric CDFs was 5:l (Hites 1990). Therefore, dry deposition is more important than wet deposition for removal of atmospheric CDFs. Both particulate and gas phase compounds can be removed from the atmosphere by wet deposition. Particle-scavenging is the process by which rainfall removes particles from the atmosphere. About 40% of tetraCDF and pentaCDF homologues, and 80% of the hexaCDF through octaCDF homologues in Bloomington, Indiana, air were removed by particle scavenging. Therefore, particle scavenging during wet deposition is generally a more important process than gas scavenging (Eitzer and Hites 1989a; Hites 1990). Wet deposition of vapor phase CDFs is a relatively minor loss process (Atkinson 1991).

In addition to the intermedia transport of CDFs from air to water and soil, intramedia transport of CDFs is also significant. It has been estimated that the lifetimes of all particulate phase CDFs and the vapor phase tetra- and higher CDFs are >l0 days. Therefore, vapor and particulate phase CDFs containing four or more chlorine atoms are expected to have sufficiently long lifetimes to undergo long-range transport (Atkinson 1991). Several authors have experimentally observed this expected long range transport of CDFs (Czuczwa et al. 1985; Oehme 1991; Rappe et al. 1989).

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The two significant processes in the transport of a chemical from water are volatilization and adsorption to sediment. The first process transfers the chemical from water to air and the second process transfers the chemical from water phase to sediment. The volatilization of CDFs from water, as with other chemicals, depends on their Henry's law constants. Since the values of the Henry's law constants for tetra- and higher CDFs are <1.48x10-^{5} atm-m^{3}/mol (see Table 3-2), the rate of volatilization of these CDFs is slow and is controlled by slow diffusion through air (Thomas 1982). The volatilization rates are further decreased because the CDFs are present in water predominantly in the adsorbed states. However, no experimental data pertaining to the volatilization of CDFs from water were located. The adsorption of CDFs to suspended solids and sediment in water depends on their K_{OC} values. The estimated log K_{OC} values for 2,3,7,8-TCDD and octaCDF are 5.61 and 8.57, respectively (see Table 3-2). Therefore, these compounds strongly adsorb to suspended solids and sediment in water. As a result, almost all the literature provides concentrations of CDFs in sediment ~- and not in water; concentration in water is so low that it is rarely measured. Therefore, sediments are the ultimate environmental sinks for CDFs (Czuczwa and Hites 1986b).

The estimated high log K_{OW} values for 2,3,7,8-tetraCDF and octaCDF (see Table 3-2) suggest that the bioconcentration of CDFs in aquatic organisms is high. The experimental bioconcentration factor for octaCDF in the guppy (*Poecilia reticulata*) was 589 on wet weight basis and 7,760 on lipid weight basis (Frank and Schrap 1990). Similarly, steady-state concentrations of slightly >0.00l μg/g (wet weight) in tissues were found in guppies after feeding the fish 10.6-40.6 μg/g octaCDF in food (Clark and Mackay 1991). In a static laboratory test, the determined bioconcentration factors for 1,2,3,7,8-pentaCDF and 2,3,4,7,8-pentaCDF in guppies were 2,400 and 5,000, respectively (Opperhuizen and Sijm 1990). In another laboratory experiment, the determination of bioconcentration of 2,3,7,8-tetraCDF in gold fish (*Carassius auratus*) was attempted by exposing the fish to fly ash (containing <1,400 ppt 2,3,7,8-tetraCDF) and contaminated sediment (containing <68 ppt 2,3,7,8-tetraCDF) in aquaria for 10 weeks (O'Keefe et al. 1986). Fish in both tests contained only 0.7 ppt 2,3,7,8-tetraCDF. The bioconcentration factor could not be determined because the concentration of 2,3,7,8-tetraCDF in water was too low. Laboratory experiments in fish exposed to contaminated sediments and in Wisconsin River fish showed that residues of 2,3,7,8-substituted congeners of CDFs are selectively enriched in carp (*Cyprinus carpio*) (Kuehl et al. 1987). Since the concentrations of CDF isomers were too low for determination, the authors reported the following bioavailability indices (ratio of concentration of a compound in fish lipid to concentration in sediment based on carbon content): 0.06 for 2,3,7,8-tetraCDF, 0.21 for 2,3,4,7,8-pentaCDF, 0.033 for

1,2,3,6,7,8-hexaCDF, and 0.0033 for 1,2,3,4,6,7,8-heptaCDF (Kuehl et al. 1987). In another study, highest bioavailable indices were achieved for organisms filtering or ingesting organic particles (mussels, chironomids) and those consuming benthic organisms (crayfish suckers) (Muir et al. 1992).

It is clear from the above experiments that the bioconcentration factors for CDFs in aquatic organisms are much lower than other polychlorinated aromatic compounds such as octachlorobiphenyl (Clark and Mackay 1991). Several explanations have been proposed to explain the lower than expected bioconcentration of CDFs in fish. One possible explanation is the rapid depuration (elimination) of the chemicals from fish, probably via biotransformation through a cytochrome P-450 system mediated MFO with the formation and elimination of polar metabolites, such as hydroxylated compounds (Frank and Schrap 1990; Opperhuizen and Sijm 1990). Another explanation for the low bioconcentration factor is a low rate of membrane permeation of these highly hydrophobic compounds (Opperhuizen and Sijm 1990). The theory of low permeation is disputed by other investigators (Frank and Schrap 1990). In addition, CDF congeners are present in the water mostly in the adsorbed state and the inability to distinguish between the adsorbed and free CDFs (bioavailability will be lower in the adsorbed state) may have largely overestimated the dissolved CDFs in water. As a result, the bioconcentration factor derived from the overestimated water concentration may be responsible for underestimating the true bioconcentration potential. More reliable estimates of bioconcentration factors may be obtained when the methods for measuring dissolved and sorbed chemical fractions in water improve (Frank and Schrap 1990).

Compared to other aquatic organism such as fish, crabs lack the ability to metabolize most of the CDF isomers (Oehme et al. 1990). The concentrations of 2,3,7,8-tetra-, 2,3,4,7,8-penta-, and 1,2,3,6,7,8-hexaCDFs in the hepatopancreas of crabs collected from a contaminated river were 2.3, 1.6, and 4.6 ppb. These values are ≈3 orders of magnitude higher than those found in fish (see Kuehle et al. 1987). Therefore, bioconcentration of CDFs in crabs will be much higher than in fish that are known to metabolize CDFs, but no values for bioconcentration of CDFs in crabs were provided (Oehme et al. 1990). Apparently this is due to lack of data concerning the concentrations of CDFs in water.

The biomagnification of CDFs in a littoral food chain consisting of phytoplankton → blue mussel (*Mytilus edulis*) → juvenile eider duck (*Somateria mollissima*) and a pelagic food chain consisting of phytoplankton → zooplankton → herring (*Clupea harengus*) → cod (*Gadus morrhua*) was studied (Broman et al. 1992). It was concluded that the total concentrations of 2,3,7,8-substituted CDFs

decreased with increasing trophic level, whereas the toxic content of the 2,3,7,8-substituted CDFs increased with increasing trophic level. The result implied a selective enrichment of 2,3,7,8-substituted isomers with high toxic equivalency factors.

The transport of CDFs from soil to air is possible via volatilization and by wind blown dusts. The very low vapor pressures and high soil sorption coefficients of those CDFs for which data are available (see Table 3-2) indicate that volatilization of these compounds from soil is insignificant (Hutzinger et al. 1985b). The observation that essentially no loss of 2,3,7,8-TCDD, a structurally similar compound, from the contaminated soil at Times Beach, Missouri, occurred in 4 years (Yanders et al. 1989), strongly suggests that volatilization is insignificant for CDFs as well. No evidence of appreciable loss of CDFs due to volatilization was found in contaminated soils during a period of 8 years (Hagenmaier et al. 1992). CDFs may be transported from soil to water via leaching and runoff. Soil leaching experiments indicate that CDFs remain strongly adsorbed even in sandy soil and leaching of these compounds from soil by rainwater is not significant (Carsch et al. 1986). The vertical movement of CDFs was found to be very slow and >90% of CDFs were found in the top 10 cm after 3 years (Hagenmaier et al. 1992). Therefore, transport of CDF from landfill soil to adjacent land or surface water by runoff water is more likely than leaching. Leaching or vertical movement of CDFs in soil can occur under special conditions, such as saturation of the sorption sites of the soil matrix, presence of organic solvents in the soil facilitating co-solvent action, cracks in the soil, or burrowing activity of animals (Hagenmaier et al. 1992; Hutzinger et al. 1985b).

Data regarding the translocation of CDFs from the roots to the above-ground parts of plants were not located. Because there is little bioaccumulation of CDDs in plants from soil (EPA 1986a), bioaccumulation of CDFs in plants is also probably insignificant. As in the case with CDDs (EPA 1986a), due to absorption by underground roots of some plants such as carrots, the roots can accumulate more CDFs, compared to aerial parts. In most plants (plants with higher aerial surface area and leaf surfaces with compounds that enhance adsorption), higher concentrations of CDFs are likely to be found on aerial portions of plants due to deposition of airborne particles and vapor. The estimated accumulation potential of CDFs on pine needles (ratio of CDF concentration in a gram of pine needles or concentration in a gram of air) due to deposition of airborne particles for 10 months was 10^4 to 10^5 (Reisch et al. 1989).

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The biotransfer of CDFs from contaminated soil to grazing animals was studied with chickens as a model (Petreas et al. 1991). Compared to controls, the concentration of CDFs in eggs of exposed chickens increased 10-fold at low exposure levels (total CDF concentration in soil was 555 ppt) and l00-fold at high exposure levels (total CDF concentration was 11,841 ppt). The biotransfer factors (ratio of concentration in egg fat over concentration in soil) for different congeners of CDFs were <l. However, statistically significant ($p<0.05$) concentration dependence of biotransfer factors, as a result of high and low exposure, were found for only 2,3,7,8-tetraCDF and 1,2,3,4,7,8,9-heptaCDF.

5.3.2 Transformation and Degradation

5.3.2.1 Air

The loss of vapor phase CDFs by reactions with HO_2 radicals, NO_3 radicals and ozone has been estimated to be of negligible importance in the troposphere (Atkinson 1991). The estimated rate constants for the reactions of vapor phase CDFs with OH radicals are as follows ($-l0^{-12}$ cm^3/molecule-sec): tetraCDFs, 1.4-8.3; pentaCDFs, 1.0-4.3; hexaCDFs, 0.74-2.6; heptaCDFs, 0.53-0.92; and octaCDFs, 0.39. Using a 12-hour average daytime hydroxyl radical concentration of $1.5x10^6/cm^3$, the estimated tropospheric lifetimes of tetra-, penta-, hexa-, hepta-, and octaCDF are 1.9-11, 3.6-15, 5.9-22, 17-31, and 39 days, respectively. The vapor phase reaction of CDFs with hydroxyl radicals is the dominant loss process and this loss process is more important for the lower, than the higher, chlorinated congeners, because the lifetimes due to this reaction are shorter for lower chlorinated congeners and the vapor phase concentrations of lower chlorinated congeners are higher. Based on the available information, the reactions of hydroxyl radicals with particulate phase CDFs are insignificant and the principal air removal mechanism for CDFs is wet and dry deposition.

Photodegradation of CDFs bound to atmospheric particles is not an important process in removing these compounds from air (Koester and Hites 1992). No data regarding vapor phase photolysis of CDFs were located. In the absence of data, the half-lives of these compounds in the vapor phase have been estimated from aqueous phase photolysis data and it was concluded that photolysis is relatively unimportant, even when compared to reaction with hydroxyl radicals (with the possible exception of 1,3,6,8-tetraCDF) (Atkinson 1991).

5.3.2.2 Water

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The loss of CDFs in water by abiotic processes such as hydrolysis and oxidation is not likely to be significant (EPA 1986a). The photolysis of CDFs in solution indicates that significant photolysis occurs in hydrogen donating solvents. Photolysis was faster in methanol than in hexane. Photolysis in these solvents proceeds with rapid dechlorination and eventual formation of unidentified resinous polymeric products (Hutzinger et al. 1973). Photolysis may proceed at a much faster rate at shorter wavelengths (254 nm) than are available from sunlight (>290 nm). It was also concluded that the rate of photolysis in hexane is faster for CDFs than CDDs and that the higher chlorinated congeners photodegrade faster than lower chlorinated congeners (Muto and Takizawa 1991). The rates of photolysis of 2,3,7,8-substituted congeners in solution are faster than the rates of non-2,3,7,8-substituted congeners (Tysklind and Rappe 1991). During the photolysis of octaCDF in dioxane under xenon lamp, hexa- and pentaCDFs were the major products, with small amounts of hepta- and tetraCDFs (Koshioka et al. 1987).

The estimated photolysis lifetimes of CDDs by sunlight in surface waters at 40° latitude range from 0.4 to 225 days, depending upon the specific congener and the season of the year (shorter lifetimes in summer than in winter) (Atkinson 1991). If the photolysis rates of CDFs are assumed to be faster than CDDs (Muto and Takizawa 1991), the photolysis lifetimes of CDFs are expected to be shorter than those for CDDs. However, the persistence of CDFs in natural water (based on a half-life of 1 year for CDDs in a model aquatic ecosystem) (EPA 1986a), contradicts the estimated photolytic lifetimes in natural water. This discrepancy is possibly due to the fact that CDDs/CDFs in natural water are present predominantly in particulate-sorbed phase. The rate of photolysis is much slower in the sorbed phase compared to solution phase photolysis (the estimated lifetimes data of Atkinson [1991] is based on solution phase photolysis) (Tysklind and Rappe 1991).

No data in the literature indicate that biodegradation of CDFs in water is significant. Biodegradation studies in sediments of a lake water indicate that 2,3,7,8-TCDD resists biodegradation (EPA 1986a). Therefore, biodegradation of CDFs in water may also be insignificant.

5.3.2.3 Sediment and Soil

The photodegradation of thin film CDIs of fly ash bound CDFs under sunlight was much slower than solution phase photolysis (Hutzinger et al. 1973; Tysklind and Rappe 1991). Direct evidence of sunlight initiated photolysis of CDFs in soil was not located. Given the fact that sunlight cannot

penetrate beyond the surface layer of soil and the lack of photolysis of CDFs adsorbed to fly ash (Koester and Hites 1992; Tysklind and Rappe 1991), the photolysis of CDFs in soil and sediment may not be significant. It may be significant for airborne particles.

No significant changes in the concentration patterns of homologous or isomeric CDFs could be detected in contaminated soil samples taken in 1981, 1987, and 1989 at the same sites and from the same depth (Hagenmaier et al. 1992). This underlines the persistence of CDFs in soil. No direct evidence was located in the literature suggesting that biodegradation of CDFs in soil and sediments is significant. The lack of biodegradation of CDDs in soil and sediments (although a few microbes degraded 2,3,7,8-TCDD at a slow rate) (EPA 1986a) and the lack of evidence for any degradation of CDFs in dated lake sediments (Czuczwa et al. 1985; Czuczwa and Hites 1986) indirectly suggest that biodegradation of CDFs in soil or sediments is not significant.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

The levels of CDFs determined in the ambient air in North America are presented in Table 5.3. As expected, the concentrations of CDFs in air show geographical variability based on the sources of emissions. Generally, the levels show the following trend: industriavauto tunnel > urban > suburban > rural (Eitzer and Hites 1989a). Even in a particular area, the level shows daily and seasonal variability. For example, the concentrations of CDFs are generally higher on rainy days with high humidity and on less windy days *(*Nakano et al. 1990). The levels are also higher *in* winter than in summer, due to increases in the contribution from combustion sources (heating) (Hunt et al. 1990). Table 5-3 indicates that the concentrations of total tetra-, penta-, hexa-, hepta-. and octaCDFs in ambient urban/suburban air can vary within the ranges of 0.13-7.34, 0.09-5.10, <0.09-12.55, 0.08-12.71, and 0.13-3.78 pg/m^3, respectively. In rural areas, the concentrations of total tetra-, penta-, hexa-, hepta-, and octaCDFs are below their detection limits. It has also been determined that the vapor/particulate phase ratio of the CDFs in ambient air depends on the season of the year and the number of chlorine substituents. Generally, the terra- and pentaCDFs are present at higher ratios in the vapor phase, while hepta- and octaCDF are present predominantly in the particulate phase in the atmosphere. This ratio of vapor/particulate phase increases during summer, compared to winter (Eitzer and Hites 1989a; Hunt et al. 1990; Nakano et al, 1990). The congener profile in the atmosphere

TABLE 5-3. Concentrations of CDFs in Ambient Indoor and Outdoor Air in North America

Site	Sampling year	CDF	Concentration (pg/m^3)	Reference
Bridgeport, CT (outdoor)	1987–1988	2,3,7,8-tetraCDF	0.078	Hunt and Maisel 1990
		total tetraCDF	0.856	
		1,2,3,7,8-pentaCDF	0.031	
		2,3,4,7,8-pentaCDF	0.047	
		total pentaCDF	0.547	
		1,2,3,4,7,8-hexaCDF	0.106	
		1,2,3,6,7,8-hexaCDF	0.039	
		2,3,4,6,7,8-hexaCDF	0.087	
		1,2,3,7,8,9-hexaCDF	0.007	
		total hexaCDF	0.580	
		1,2,3,4,6,7,8-heptaCDF	0.212	
		1,2,3,4,7,8,9-heptaCDF	0.033	
		total heptaCDF	0.369	
		octaCDF	0.211	
Toronto Island, Canada (outdoor)	1988–1989	total tetraCDF	0.404	Steer et al. 1990
		total pentaCDF	0.118	
		total hexaCDF	0.204	
		total heptaCDF	0.240	
		octaCDF	0.142	
Dorset, Canada (outdoor)	1988–1989	total tetraCDF	0.164	Steer et al. 1990
		total pentaCDF	0.200	
		total hexaCDF	0.074	
		total heptaCDF	0.52	
		octaCDF	0.194	
Windsor, Canada (outdoor)	1988–1989	total tetraCDF	0.733	Steer et al. 1990
		total pentaCDF	0.383	
		total hexaCDF	0.333	
		total heptaCDF	0.550	
		octaCDF	0.182	
Boston, MA office building (indoor)	No data	2,3,7,8-tetraCDF	(0.37)[a]–1.4	Komsky and Kuoka 1989
		total tetraCDF	(0.64)[a]–6.2	
		total pentaCDF	(0.12)[a]–1.9	
		total hexaCDF	(0.39)–(1.5)[a]	
		octaCDF	(0.54)–(1.8)[a]	
Albany, NY (outdoor)	1987–1988	total tetraCDF	3.86	Smith et al. 1990
		2,3,7,8-tetraCDF/unknown isomer	0.89	
		total pentaCDF	2.00	
		total hexaCDF	0.28	
		total heptaCDF	<0.34	
		octaCDF	<0.50	
Binghamton, NY (outdoor)	1988	total tetraCDF	0.94	Smith et al. 1990
		2,3,7,8-tetraCDF/unknown isomer	0.18	
		total pentaCDF	0.25	
		total hexaCDF	<0.09	
		total heptaCDF	<0.14	
		octaCDF	<0.30	

TABLE 5-3. Concentrations of CDFs in Ambient Indoor and Outdoor Air in North America (*continued*)

Site	Sampling year	CDF	Concentration (pg/m^3)	Reference
Utica, NY (outdoor)	1988	total tetraCDF	7.34	Smith et al. 1990
		2,3,7,8-tetraCDF/unknown isomer	1.15	
		total pentaCDF	3.16	
		total hexaCDF	<0.36	
		total heptaCDF	<0.24	
		octaCDF	<0.61	
Niagara Falls, NY (outdoor)	1987–1988	total tetraCDF	1.53	Smith et al., 1990
		2,3,7,8-tetraCDF/unknown isomer	<0.11	
		total pentaCDF	0.98	
		total hexa CDF	1.45	
		total heptaCDF	1.37	
		octaCDF	0.51	
United States and Canada ambient air (outdoor)	No data	total tetraCDF	1.09	Waddell et al., 1990
		total pentaCDF	0.63	
		total hexa CDF	0.72	
		total heptaCDF	1.14	
		octaCDF	0.62	
Bloomington, IN	1986	2,3,7,8-/2,3,4,8-/2,3,4,6-tetraCDF	0.048	Eitzer and Hites 1989b
		total tetraCDF	0.263	
		1,2,3,7,8-/1,2,3,4,8-pentaCDF	0.017	
		2,3,4,7,8-/1,2,3,6,9-pentaCDF	0.017	
		total pentaCDF	0.20	
		1,2,3,4,7,8-/1,2,3,4,6,7-hexaCDF	0.023	
		1,2,3,6,7,8-/1,2,3,4,7,9-hexaCDF	0.016	
		2,3,4,6,7,8-hexaCDF	0.015	
		1,2,3,7,8,9-hexaCDF	0.0007	
		total hexaCDF	0.113	
		1,2,3,4,6,7,8-heptaCDF	0.039	
		1,2,3,4,7,8,9-heptaCDF	0.005	
		total heptaCDF	0.071	
		octaCDF	0.028	
Southern California (outdoor)	1987–1989	2,3,7,8-tetraCDF	<0.007–0.482	Hunt et al. 1990
		1,2,3,7,8-pentaCDF	<0.010–1.9	
		2,3,4,7,8-pentaCDF	<0.009–0.110	
		1,2,3,4,7,8-hexaCDF	<0.001–0.27	
		1,2,3,6,7,8-hexaCDF	<0.001–0.800	
		2,3,4,6,7,8-hexaCDF	<0.001–0.280	
		1,2,3,4,6,7,8-heptaCDF	<0.002–1.58	
		1,2,3,4,7,8,9-heptaCDF	<0.002–0.092	

TABLE 5-3. Concentrations of CDFs in Ambient Indoor and Outdoor Air in North America (*continued*)

Site	Sampling year	CDF	Concentration (pg/m^3)	Reference
Los Angeles,, CA (outdoor)	1987	2,3,7,8-tetraCDF	0.021	Maisel and Hunt 1990
		other tetraCDF	0.30	
		1,2,3,7,8-pentaCDF	0.077	
		2,3,4,7,8-pentaCDF	0.077	
		other pentaCDF	0.41	
		1,2,3,4,7,8-hexaCDF	0.151	
		1,2,3,6,7,8-hexaCDF	0.25	
		2,3,4,6,7,8-hexaCDF	<0.069	
		1,2,3,7,8,9-hexaCDF	<0.083	
		other hexaCDF	<0.080	
		1,2,3,4,6,7,8-heptaCDF	<0.190	
		1,2,3,4,7,8,9-heptaCDF	<0.018	
		other heptaCDF	0.26	
		octaCDF	0.056	
Dayton, OH (outdoor—suburban/roadside)	1988	total tetraCDF	0.13	Tieman et al. 1989
		total pentaCDF	0.24	
		total hexaCDF	0.14	
		total heptaCDF	0.11	
		octaCDF	<0.07	
Dayton, OH (outdoor—municipal solid waste incinerator)	1988	total tetraCDF	1.23	Tieman et al. 1989
		2,3,7,8-tetraCDF	0.11	
		total pentaCDF	5.10	
		1,2,3,7,8-pentaCDF/unknown isomer	0.46	
		2,3,4,7,8-pentaCDF	0.53	
		total hexaCDF	12.55	
		1,2,3,4,7,8-hexaCDF/unknown isomer	1.18	
		1,2,3,6,7,8-hexaCDF	2.27	
		1,2,3,7,8,9-hexaCDF	<0.06	
		2,3,4,6,7,8-hexaCDF	<0.41	
		total heptaCDF	12.71	
		1,2,3,4,6,7,8-heptaCDF	8.22	
		1,2,3,4,7,8,9-heptaCDF	0.56	
		octaCDF	3.78	
Dayton, OH (outdoor—rural area)	1988	total tetraCDF	<0.02	Tieman et al. 1989
		total pentaCDF	<0.02	
		total hexaCDF	<0.05	
		total heptaCDF	<0.07	
		octaCDF	<0.17	
Windsor, Canada (outdoor)	1987–1988	total tetraCDF	0.21	Bobet et al. 1990
		total pentaCDF	0.09	
		total hexaCDF	0.10	
		total heptaCDF	0.08	
		octaCDF	0.13	
Walpole Island, Canada (outdoor)	1987–1988	total tetraCDF	<0.05	Bobet et al. 1990
		total pentaCDF	<0.07	
		total hexaCDF	<0.10	
		total heptaCDF	<0.07	
		octaCDF	<0.14	

TABLE 5-3. Concentrations of CDFs in Ambient Indoor and Outdoor Air in North America (*continued*)

Site	Sampling year	CDF	Concentration (pg/m^3)	Reference
Lake Trout, WI (outdoor)	1987	total tetraCDF	0.083	Edgarton et al. 1989
		total pentaCDF	0.067	
		total hexaCDF	0.031	
		total heptaCDF	0.012	
		octaCDF	0.006	
Akron, OH (outdoor)	1987	2,3,7,8-tetraCDF	0.200	Edgarton et al. 1989
		total tetraCDF	1.23	
		1,2,3,7,8-pentaCDF	0.029	
		2,3,4,7,8-pentaCDF	0.036	
		total pentaCDF	0.590	
		1,2,3,4,7,8-hexaCDF	0.083	
		1,2,3,6,7,8-hexaCDF	0.065	
		2,3,4,6,7,8-hexaCDF	<0.021	
		1,2,3,7,8,9-hexaCDF	0.032	
		total hexaCDF	0.620	
		1,2,3,4,6,7,8-heptaCDF	0.237	
		1,2,3,4,7,8,9-heptaCDF	<0.029	
		total heptaCDF	0.383	
		octaCDF	0.180	
Columbus, OH (outdoor)	1987	2,3,7,8-tetraCDF	0.405	Edgarton et al. 1989
		total tetraCDF	2.85	
		1,2,3,7,8-pentaCDF	0.045	
		2,3,4,7,8-pentaCDF	<0.056	
		total pentaCDF	0.995	
		1,2,3,4,7,8-hexaCDF	0.165	
		1,2,3,6,7,8-hexaCDF	0.141	
		2,3,4,6,7,8-hexaCDF	<0.02	
		1,2,3,7,8,9-hexaCDF	0.079	
		total hexaCDF	0.785	
		1,2,3,4,6,7,8-heptaCDF	0.335	
		1,2,3,4,7,8,9-heptaCDF	<0.021	
		total heptaCDF	0.450	
		octaCDF	<0.260	
Waldo, OH (outdoor)	1987	2,3,7,8-tetraCDF	0.130	Edgarton et al. 1989
		total tetraCDF	0.890	
		1,2,3,7,8-pentaCDF	0.021	
		2,3,4,7,8-pentaCDF	<0.033	
		total pentaCDF	0.500	
		1,2,3,4,7,8-hexaCDF	0.098	
		1,2,3,6,7,8-hexaCDF	0.014	
		2,3,4,6,7,8-hexaCDF	<0.008	
		1,2,3,7,8,9-hexaCDF	0.097	
		total hexaCDF	0.510	
		1,2,3,4,6,7,8-heptaCDF	0.220	
		1,2,3,4,7,8,9-heptaCDF	0.019	
		total heptaCDF	0.290	
		octaCDF	0.077	

[a]Detection limit

follows the congener profile of their sources, that is, if the major source of CDFs in the atmosphere is a municipal incinerator, the congener pattern in the air follows the congener pattern in flue gas from that municipal incinerator (Edgerton et al. 1989; Eitzer and Hites 1989a).

The majority of CDFs found in the air are non-2,3,7,8-substituted congeners, which are much less toxic than 2,3,7,8-substituted congeners. Among the 2,3,7,8-substituted isomers in the air, the 1,2,3,4,6,7,8-heptaCDF congener dominates, followed by 2,3,7,8-tetraCDF. It has been shown that 2,3,7,8-tetraCDF constitutes ≈9% of total tetraCDFs; 1,2,3,7,8-penta- and 2,3,4,7,8-pentaCDF constitute ≈9% and 10.4%, respectively, of total pentaCDFs; 1,2,3,4,7,8-hexa-, and 1,2,3,6,7,8-hexaCDF constitute ≈9.4% and 18.1%, respectively, of the total hexaCDFs; and 1,2,3,4,6,7,8-heptaand 1,2,3,4,7,8,9-heptaCDF constitute ≈64.7% and 4.4%, respectively, of the total heptaCDFs present in the air near a municipal solid waste incinerator in Dayton, Ohio (Tiernan et al. 1989).

Considerably higher concentrations of CDFs have been detected in the indoor air and wipe samples of buildings after accidental fires involving PCB capacitors/transformers. For example, the concentrations of total CDFs and 2,3,7,8-tetraCDF (plus co-eluting isomers) in wipe samples from the transformer vault after the 1983 transformer fire in Chicago were 12,210 and 410 ng/l00 cm^2, respectively (Hryhorczuk et al. 1986). The concentrations of total tetraCDFs in air and wipe samples inside the vault 4 months after the 1983 San Francisco transformer fire were l,000-3,000 pg/m^3 and l,000-23,000 ng/l00 cm^2, respectively (Stephens 1986). Seven months following the fire, the maximum concentration of 2,3,7,8-substituted CDFs in air of the building that contained the transformer vault was 19.5 pg/m^3. The concentrations of total tetraCDFs, 2,3,7,8-tetraCDF (plus co-eluting isomers) and total pentaCDFs of indoor air in a Binghamton, New York, office building 1.5-2 years after cleanup following a 1981 electric fire were ≤23, 195, and 60 pg/m^3, respectively (Smith et al. 1986). Similarly, concentrations of tetraCDF, pentaCDF, hexaCDF, heptaCDF and octaCDF ≤0.4, 0.6, 2.2, 4.4, and 4.8 ng/l00 cm^2, respectively, were present in the wipe samples of a building used for the improper incineration of PCBs over 12 years ago (Thompson et al. 1986).

5.4.2 Water

The concentrations of CDFs in most waters are so low that it is difficult to determine the levels in drinking water and surface water, unless the surface water is sampled close to points of effluent discharge containing CDFs. Because of their low water solubilities and high K_{OC} values, the CDFs

partition from the water to sediment in environmental water or in sludge during the treatment of waste waters. Therefore, more monitoring data are available for CDFs levels in the latter two media.

A drinking water sample in Sweden contained 2,3,4,7,8-pentaCDF at a concentration of 0.002 ppq (Rappe 1991). The levels of CDFs in drinking water from 20 communities in New York state were measured (Meyer et al. 1989). Total tetraCDFs at a concentration of 2.6 ppq (pg/L) and octaCDF at a concentration 0.8 ppq are the only two congener groups detected in 1 of 20 water supplies (Lockport, New York). The concentration of 2,3,7,8-tetraCDF in water from Lockport was 1.2 ppq. The raw water that served as the source of this drinking water contained several CDFs at the following concentrations (ppq): total tetraCDF, 18.0; 2,3,7,8-tetraCDF, not detected (detection limit 0.7); 1,2,3,7,8-pentaCDF, 2.0; total pentaCDF, 27.0; 1,2,3,4,7,8-hexaCDF, 39.0; 1,2,3,6,7,8-hexaCDF, 9.2; total hexaCDF, 85.0; 1,2,3,4,6,7,8-heptaCDF, 210; total heptaCDF, 210; and octaCDF, 230. Since the finished drinking water contained 2,3,7,8-tetraCDF, and the raw water did not contain any detectable level of this compound, the source of 2,3,7,8-tetraCDF in the drinking water must be the chlorination process. Considerably higher concentrations of CDFs were detected in the sediment of the raw water. This provides more indirect evidence that chlorination may be partially responsible for the *in situ* production of CDFs.

Effluents from bleached kraft and sulfite mill pulp in the United States, Canada, and Europe contained total tetraCDFs in the concentration range of <0.01-4,100 ppt, whereas the concentrations of 2,3,7,8-tetraCDF varied from <0.002 to 8.4 ppt. The octaCDF levels in these effluents ranged from <0.05 to 0.5 ppt. The sludge from the treated effluents from paper mills contained much higher concentrations of CDFs. In one case, the sludge from a chloralkali process contained ≤52,000 ppt of 2,3,7,8-tetraCDF and 81,000 ppt of octaCDF (Clement et al. 1989a, 1989b; Rappe et al. 1990a; Waddell et al. 1990; Whitmore et al. 1990).

Surface water adjacent to a landfill near Tonawanda, New York, contained the following concentrations of CDFs (ppt): total tetraCDFs, 0.2-77; total pentaCDFs, 0.3-130; total hexaCDFs, 0.8-200; total heptaCDFs, 1.0-980; and octaCDF, 1.2-1,500 (Clement et al. 1989c). Leachates from bottom and fIy ash disposal facilities of five state-of-the-art mass burn municipal waste combustors, with a variety of pollution control equipment, were analyzed for CDFs. With the exception of the leachate from one facility, leachates from four other facilities contained CDFs below the detection

level (0.01-0.06 ppb). HeptaCDF at a concentration of 0.076 ppb was detected in the remaining leachate sample (EPA 1990).

The level of CDFs has also been determined in rain water. The concentrations of total tetraCDFs, total pentaCDFs, total hexaCDFs, total heptaCDFs and octaCDF in rain water from Bloomington, Indiana; Dorset, Canada; and Toronto, Canada, ranged from <0.6 to 5.7, 0.2 to 6.0, 0.7 to 6.0, <0.8 to 2.4, and <0.8 to 0.8 ppq, respectively (Eitzer and Hites 1989b; Reid et al. 1990). As expected, the concentrations of CDFs were lower in rain water from the rural site (Dorset) than from the urban site (Toronto) (Reid et al 1990). The levels of CDFs in fog have also been determined, and the congener profile was similar to rain water; however, the concentrations of CDFs were higher in fog than in rain water, due to enhanced particle scavenging by fog (Czuczwa et al. 1989).

5.4.3 Sediment and Soil

The maximum 2,3,7,8-tetraCDF and 2,3,7,8-substituted CDF concentrations of 0.3 ppt (ng/kg) and 11.0 ppt, respectively, were determined for sediments from an uncontaminated river (Elk River) in Minnesota (Reed et al. 1990). The maximum concentrations of total pentaCDFs, hexaCDFs, heptaCDFs, and octaCDF in sediment samples from the same river were 25.0, 12.0, 30.0, and 23.0 ppt, respectively. In all cases, the analyte was not detected in some samples. The concentrations of 2,3,7,8-tetraCDF in sediment from the lower Hudson River (New York), Cuyahoga River (Ohio), Menominee River (Wisconsin), Fox River (Wisconsin), Raisin River (Michigan), and Saginaw River (Wisconsin) ranged from 5 to 97 ppt (O'Keefe et al. 1984; Smith et al. 1990b). The concentration of 2,3,7,8-tetraCDF in sediment from an uncontaminated lake (Lake Pepin) in Wisconsin was <l ppt, while its concentration in sediment from Lake Michigan in Green Bay (Wisconsin) was 24 ppt (Smith et al. 1990a). The concentrations of 2,3,7,8-tetraCDF in estuarine sediment varied from 15.0 ppt for an uncontaminated sediment in Long Island Sound (New York) to 4,500 ppt in sediment from an estuary adjacent to a 2,4,5- production facility in Newark, New Jersey (Bopp et al. 1991; Norwood et al. 1989). A concentration ≤1,400 ppt was also detected in sediment from New Bedford Harbor (Massachusetts) near a Superfund site (Norwood et al. 1989). The concentrations of 2,3,7,8-tetraCDF and other 2,3,7,8-substituted congeners of pentaCDF were higher in contaminated sediments than uncontaminated sediments (Norwood et al. 1989). In a survey of harbor sediment near a wood treatment facility at Thunder Bay (Ontario), the concentration of tetraCDFs and pentaCDFs were below

the detection limit, while the levels of the higher congeners increased with the degree of chlorination (maximum of 6.5 ng/g for H_6CDF to 400 ng/g for O_8CDF) (McKee et al. 1990).

The concentrations (ppt) of CDFs in uncontaminated soils from the vicinity of Elk River, Minnesota were as follows (detection limit in parentheses): 2,3,7,8-tetraCDF, not detected (0.8); total tetraCDF, not detected (0.8) to 1.2; total hexaCDFs, 6.7-150; 1,2,3,4,6,7,8-heptaCDF, 26-72; total heptaCDFs, 30-260; and octaCDF, not detected (3) to 270 (Reed et al. 1990). The concentrations (ppt) of CDFs in soils adjacent to a refuse incineration facility in Hamilton, Ontario, were as follows (detection limit in parenthesis): total tetraCDFs, not detected (0.3) to 71; total pentaCDFs, not detected (1.3) to 6.0; total hexaCDFs, not detected (1.3); total heptaCDFs, not detected (1.3) to 180; and octaCDF, not detected (0.8) to 811 (McLaughlin et al. 1989). These levels were not elevated compared to urban control samples. Similarly, the levels of CDFs in soils adjacent to a municipal incinerator in England were indistinguishable from background levels (Mundy et al. 1989). On the other hand, much higher levels of CDFs were detected in soils from PCP-containing waste landfill in Germany. For example, the concentrations (ppt) of CDFs in the landfill soil were as follows: 1,2,3,7,8/1,2,3,4,8-pentaCDF, 17,000; 2,3,4,7,8-pentaCDF, 7,000; 1,2,3,4,7,8/1,2,3,4,7,9-hexaCDF, 152,000; 1,2,3,6,7,8-hexaCDF, 48,000; 1,2,3,7,8,9-hexaCDF, 3,000; and 2,3,4,6,7,8-hexaCDF, 24,000 (Hagenmaier and Berchtold 1986).

5.4.4 Other Environmental Media

The concentrations of CDFs in meat, fish, and dairy products purchased from a supermarket in upstate New York were 0.14-7.0, 0.07-1.14, and 0.3-5 ppt (wet weight), respectively (Schecter et al. 1993). The concentrations of 2,3,7,8-TCDF in these meat, fish, and dairy products were 0.01-0.1, 0.02-0.73, and 0.02-0.15 ppt (wet weight), respectively (Schecter et al. 1993).

A large number of data concerning the levels of CDFs in fish collected from different waters are available (De Vault et al. 1989; Gardner and White 1990; O'Keefe et al. 1984; Petty et al. 1983; Smith et al. 1990b; Zacharewski et al. 1989) and representative data on the concentrations of CDFs, particularly the 2,3,7,8-substituted congeners are presented in Table 5.4. It is evident from the table that 2,3,7,8-tetraCDF is the prevalent CDF congener present in fish, followed by 2,3,4,7,8-pentaCDF. The concentrations of CDFs are significantly higher in the hepatopancreas than in the meat of crabs and lobster. Among the Great Lakes, Lake Erie and Lake Superior are cleaner in

TABLE 5-4. Levels of CDFs in Fish and Other Aquatic Organisms

Species	Sampling area	CDF	Concentration (ppt [wet weight])	Reference
Striped bass (*Morone saxatilis*) meat	Newark Bay and New York Bight	2,3,7,8-tetraCDF	68.7	Rappe et al. 1991
		total tetraCDF	92.5	
		1,2,3,7,8-/1,2,3,4,8-pentaCDF	7.1	
		2,3,4,7,8-pentaCDF	30.3	
		total pentaCDF	58.5	
		1,2,3,4,7,8-/1,2,3,4,7,9-hexaCDF	1.1	
		1,2,3,6,7,8-hexaCDF	0.4	
		1,2,3,7,8,9-hexaCDF	<0.1	
		2,3,4,6,7,8-hexaCDF	<2.6	
		total hexaCDF	3.2	
		1,2,3,4,6,7,8-heptaCDF	1.6	
		1,2,3,4,7,8,9-heptaCDF	<0.4	
		octaCDF	<3.0	
Blue crab (*Callinectes sapidus*) meat	Newark Bay and New York Bight	2,3,7,8-tetraCDF	13.3	Rappe et al. 1991
		total tetraCDF	148.7	
		1,2,3,7,8-/1,2,3,4,8-pentaCDF	5.5	
		2,3,4,7,8-pentaCDF	7.3	
		total pentaCDF	91.9	
		1,2,3,4,7,8-/1,2,3,4,7,9-hexaCDF	2.6	
		1,2,3,6,7,8-hexaCDF	0.6	
		1,2,3,7,8,9-hexaCDF	<0.2	
		2,3,4,6,7,8-hexaCDF	<2.3	
		total hexaCDF	9.4	
		1,2,3,4,6,7,8-heptaCDF	3.2	
		1,2,3,4,7,8,9-heptaCDF	<0.9	
		total heptaCDF	3.2	
		octaCDF	<7.1	
Blue crab (*Callinectes sapidus*) hepatopancreas	Newark Bay and New York Bight	2,3,7,8-tetraCDF	628.3	Rappe et al. 1991
		total tetraCDF	7,049.3	
		1,2,3,7,8-/1,2,3,4,8-pentaCDF	185.7	
		2,3,4,7,8-pentaCDF	391.4	
		total pentaCDF	4,219.1	
		1,2,3,4,7,8-/1,2,3,4,7,9-hexaCDF	261.0	
		1,2,3,6,7,8-hexaCDF	43.3	
		1,2,3,7,8,9-hexaCDF	<5.0	
		2,3,4,6,7,8-hexaCDF	9.8	
		total hexaCDF	803.3	
		1,2,3,4,6,7,8-heptaCDF	184.6	
		1,2,3,4,7,8,9-heptaCDF	7.1	
		octaCDF	<51	
Lobster (*Homarus americanus*) meat	Newark Bay and New York Bight	2,3,7,8-tetraCDF	<0.3	Rappe et al. 1991
		total tetraCDF	27.1	
		1,2,3,7,8-/1,2,3,4,8-pentaCDF	2.4	
		2,3,4,7,8-pentaCDF	1.8	
		total pentaCDF	33.6	
		1,2,3,4,7,8-/1,2,3,4,7,9-hexaCDF	0.4	
		1,2,3,6,7,8-hexaCDF	<0.2	
		1,2,3,7,8,9-hexaCDF	<0.2	
		2,3,4,6,7,8-hexaCDF	<2.0	
		total hexaCDF	7.8	
		1,2,3,4,6,7,8-heptaCDF	<0.9	
		1,2,3,4,7,8,9-heptaCDF	<0.9	
		octaCDF	<7.7	

TABLE 5-4. Levels of CDFs in Fish and Other Aquatic Organisms (*continued*)

Species	Sampling area	CDF	Concentration (ppt [wet weight])	Reference
Lobster (*Homarus americanus*) hepatopancreas	Newark Bay and New York Bight	2,3,7,8-tetraCDF	365.7	Rappe et al. 1991
		total tetraCDF	1,568.6	
		1,2,3,7,8-/1,2,3,4,8-pentaCDF	79.5	
		2,3,4,7,8-pentaCDF	179.2	
		total pentaCDF	1,008.4	
		1,2,3,4,7,8-/1,2,3,4,7,9-hexaCDF	10.7	
		1,2,3,6,7,8-hexaCDF	<6.0	
		1,2,3,7,8,9-hexaCDF	<3.0	
		2,3,4,6,7,8-hexaCDF	7.0	
		total hexaCDF	172.1	
		1,2,3,4,6,7,8-heptaCDF	<3.8	
		1,2,3,4,7,8,9-heptaCDF	<3.8	
		octaCDF	<29.2	
Lobster (*Homarus americanus*) digestive gland	Mipamichi Bay and Limestone Point, New Brunswick; Sydney Harbor and Port Morien, Nova Scotia	total tetraCDF	189.8	Clement et al. 1987b
		total pentaCDF	52.2	
		total hexaCDF	37.9	
		total heptaCDF	<9.1	
		octaCDF	(2-10)[a]	
Carp (*Cyprinus carpio*) Coho salmon (*Oncorhynchus kisutch*) Lake Trout (*Salvelimus namayeush*) Bloater (*Copegonus hoyi*) Brown trout (*Salmo trutta*) Walleye trout (*Stizostedion vitreum vitreum*) (composite)	Lake Ontario	total pentaCDFs	1,015	Stalling et al. 1985
		total tetraCDFs	327	
Lake trout (*Salvelinus namaycush*) Walleye trout (*S. vitreum vitreum*) (composite)	Lake St. Clair	2,3,7,8-tetraCDF	24.8	Zacharewski et al. 1989
		1,2,3,7,8-pentaCDF	3.7	
		2,3,4,7,8-pentaCDF	5.4	
		1,2,3,4,7,8-hexaCDF	0.5	
		1,2,3,6,7,8-hexaCDF	0.5	
		1,2,3,7,8,9-hexaCDF	<0.05	
		2,3,4,6,7,8-hexaCDF	0.9	
		1,2,3,4,6,7,8-heptaCDF	0.5	
		1,2,3,4,7,8,9-heptaCDF	<0.2	
		octaCDF	0.8	
Lake trout (*Salvelinus namaycush*) Walleye trout (*S. vitreum vitreum*) (composite)	Lake Michigan	2,3,7,8-tetraCDF	34.8	Zacharewski et al. 1989
		1,2,3,7,8-pentaCDF	4.9	
		2,3,4,7,8-pentaCDF	10.2	
		1,2,3,4,7,8-hexaCDF	1.4	
		1,2,3,6,7,8-hexaCDF	1.1	
		1,2,3,7,8,9-hexaCDF	<0.05	
		2,3,4,6,7,8-hexaCDF	1.3	
		1,2,3,4,6,7,8-heptaCDF	0.9	
		1,2,3,4,7,8,9-heptaCDF	<0.2	
		octaCDF	<2.0	

TABLE 5-4. Levels of CDFs in Fish and Other Aquatic Organisms (*continued*)

Species	Sampling area	CDF	Concentration (ppt [wet weight])	Reference
Lake trout	Lake Ontario	2,3,7,8-tetraCDF	20.6	Zacharewski
(*Salvelinus namaycush*)		1,2,3,7,8-pentaCDF	4.7	et al. 1989
Walleye trout		2,3,4,7,8-pentaCDF	20.2	
(*S. vitreum vitreum*)		1,2,3,4,7,8-hexaCDF	12.7	
(composite)		1,2,3,6,7,8-hexaCDF	1.9	
		1,2,3,7,8,9-hexaCDF	<0.1	
		2,3,4,6,7,8-hexaCDF	1.2	
		1,2,3,4,6,7,8-heptaCDF	0.9	
		1,2,3,4,7,8,9-heptaCDF	<0.1	
		octaCDF	<0.9	
Lake trout	Lake Huron	2,3,7,8-tetraCDF	22.8	Zacharewski
(*Salvelinus namaycush*)		1,2,3,7,8-pentaCDF	6.2	et al. 1989
Walleye trout		2,3,4,7,8-pentaCDF	12.8	
(*S. vitreum vitreum*)		1,2,3,4,7,8-hexaCDF	1.6	
(composite)		1,2,3,6,7,8-hexaCDF	1.2	
		1,2,3,7,8,9-hexaCDF	<0.07	
		2,3,4,6,7,8-hexaCDF	1.4	
		1,2,3,4,6,7,8-heptaCDF	0.5	
		1,2,3,4,7,8,9-heptaCDF	<0.1	
		octaCDF	<0.3	
Lake trout	Lake Erie	2,3,7,8-tetraCDF	11.3	Zacharewski
(*Salvelinus namaycush*)		1,2,3,7,8-pentaCDF	1.4	et al. 1989
Walleye trout		2,3,4,7,8-pentaCDF	2.7	
(*S. vitreum vitreum*)		1,2,3,4,7,8-hexaCDF	0.2	
(composite)		1,2,3,6,7,8-hexaCDF	0.3	
		1,2,3,7,8,9-hexaCDF	<0.1	
		2,3,4,6,7,8-hexaCDF	0.5	
		1,2,3,4,6,7,8-heptaCDF	0.6	
		1,2,3,4,7,8,9-heptaCDF	<0.2	
		octaCDF	<1.1	
Lake trout	Lake Superior	2,3,7,8-tetraCDF	15.7	Zacharewski
(*Salvelinus namaycush*)		1,2,3,7,8-pentaCDF	1.7	et al. 1989
Walleye trout		2,3,4,7,8-pentaCDF	2.8	
(*S. vitreum vitreum*)		1,2,3,4,7,8-hexaCDF	0.5	
(composite)		1,2,3,6,7,8-hexaCDF	0.3	
		1,2,3,7,8,9-hexaCDF	<0.06	
		2,3,4,6,7,8-hexaCDF	0.4	
		1,2,3,4,6,7,8-heptaCDF	0.4	
		1,2,3,4,7,8,9-heptaCDF	<0.2	
		octaCDF	<0.8	

[a]Detection limit

terms of CDF contamination than the other three lakes (see Table 5-4). The mean level of total 2,3,7,8-substituted CDFs in gutted whole fish from the St. Maurice River, Quebec, caught immediately downstream of a kraft mill was 260 pg/g (ppt), but the level declined to 112 ppt at 95 km downstream (Hodson et al. 1993). Data on 2,3,7,8-substituted CDF congeners in aquatic fauna were analyzed by principal component analysis. In this method, the congener profile in aquatic fauna can be used to predict the principal source of contamination such as pulp mill effluent, deposition from combustion source, and effluent from magnesium production (Zitko 1992).

CDF levels have been determined in a multitude of environmental samples, including cork and wall paper (Frommberger 1991); foods of animal and vegetable origin (Fűrst et al. 1990; Glidden et al. 1990; Ryan et al. 1985b; Schecter et al. 1989b); commercial detergents and related products (Rappe et al. 1990b); coffee filters (Fricker and Hardy 1990; LeBel et al. 1992; Wiberg et al. 1989); several consumers products, including diapers, shopping bags, cigarette paper, tampons, and cotton (LeBel et al. 1992; Wiberg et al. 1989); paper products (LeBel et al. 1992; Keenan and Sullivan 1989); latex nipples (Gorski 1981); pine needles (Safe et al. 1992); marine mammals (Norstrom et al. 1990); and eggs of Great Blue Herons (Elliott et al. 1989). Comparison of data for bulk milk and milk in cartons indicates that 2,3,7,8-tetraCDF migrates in small amounts from some bleached paper cartons to bulk milk (Glidden et al. 1990; Ryan et al. 1992). The transfer of CDFs from cardboard and plastic-coated bleached paperboard milk cartons to bulk milk has been observed by other investigators (Beck et al. 1990; Ryan et al. 1992). The mean concentrations of tetraCDF in bond paper composite, paper towel composite, and composite diaper pulp were 265, 33, and 8 ppt, respectively (Keenan and Sullivan 1989). The concentrations of 2,3,7,8-tetraCDF in bleached coffee filters, shopping bags, and tampons were 22, 7.6, and 0.9 ppt, respectively (Wieberg et al. 1989). On the other hand, no CDFs (detection limit ≤1ppt) were detected in commercially available coffee filters in the United States (Fricker and Hardy 1990).

The percent migration of 2,3,7,8-tetraCDF from commercial articles of food contact products (e.g., milk packaged in cartons, coffee filters, paper cups and plates, popcorn bags) to foods may range from 0.1% to 35% under normal use conditions (Cramer et al. 1991). Therefore, the concentration of CDFs in packaged whole milk depends on the packaging material. Usually, commercial milk packaged in glass contains less CDFs than milk packaged in cartons (Rappe et al. 1990c). The mean concentration of 2,3,7,8-tetraCDF in whole milk packaged in cartons from California was 0.45 pg/g wet weight (Hayward et al. 1991). All other 2,3,7,8-substituted CDFs were either not detected or detected at very

low levels (Hayward et al. 1991). Commercial milk from Sweden contained significant levels of other 2,3,7,8-substituted CDFs (Rappe et al. 1990c). The intake of CDDs/CDFs from all bleached paper food-contact articles was estimated to be 8.8 pg toxic equivalent (TE)/person/day (see Section 2.4) (Cramer et al. 1991). However, with the reduction of CDD/CDF levels in paper pulp available at the present time, the exposure may be considerably less than this estimate (Cramer et al. 1991).

The levels of CDFs in the tissues of aquatic and terrestrial birds and in dolphins from contaminated areas are also available (Ankley et al. 1993; Jarman et al. 1993; Jones et al. 1993; Kuehl et al. 1991). Generally, CDDs/CDFs contribute a small portion of the total TCDD-equivalent toxicity in the aquatic birds, while most of the TCDD-equivalent toxicity is contributed by non-*ortho*-substituted PCBs. In terrestrial birds, the contribution of CDDs/CDFs towards the total TCDD-equivalent toxicity is greater than in aquatic birds (Jones et al. 1993).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is exposed to CDFs by inhalation, ingestion of drinking water, consumption of food, and through the use of certain consumer products. Since the concentrations of CDFs in ambient air and drinking water are low (see Section 5.4), the intake of CDFs by inhalation and ingestion of drinking water would be low. It has been shown that inhalation exposure was not a major pathway of human exposure to CDFs (Travis and Hattermer-Frey 1989). The estimate that inhalation exposure contributes 2% of the total average human intake of CDDs/CDFs (Hattermer-Frey and Travis 1989) has been questioned as too low by other investigators (Goldfarb and Harrad 1991). The concentrations of CDD/CDF in foods consumed by a typical German were determined, and the intake of total CDD/CDF from food expressed as TE (see Section 2.4) to 2,3,7,8-TCDD was estimated to be 1.2 pg TE/kg body weight/day (International dioxin toxic equivalent) (Fürst et al. 1990). The estimated intake of CDD/CDF from typical Canadian food was 1.5 pg TE/kg body weight/day (Birmingham et al. 1989a). From detailed determinations of the levels of TCDD/TCDF in air, water, soil, food, and consumer products in Canada, the estimated intakes of CDD/CDF were 0.07 pg TE/kg body weight/day from air, 0.002 pg TE/kg body weight/day from water, 0.02 pg TE/kg body weight/day from ingestion of soil, 2.328 pg TE/kg body weight/day from food, and 0.005 pg TE/kg body weight/day from consumer products (Birmingham et al. 1989b). Therefore, based on toxic equivalency, inhalation constitutes 2.9% of the estimated total intake, ingestion of drinking water constitutes 0.l%, ingestion of soil 0.8%, ingestion of food 96% and consumer products the residual

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0.2% of the estimated total daily intake of TCDDs/TCDFs. The estimated daily intakes of 2,3,7,8-tetraCDF and 2,3,4,7&pentaCDF in the United States are 0.05 and 0.068 ng, respectively (Graham et al. 1986), but data for the daily intake of total CDFs and all the 2,3,7,8-substituted CDFs from the different routes of exposure in the United States were not located. However, data for the daily intake of the combination of CDDs and CDFs from different exposure routes in Canada are available. The total average daily intake of CDDs/CDFs in the industrialized countries is estimated at 1.9 pg TE/kg body weight/day (Fishbein et al. 1992).

Occupational exposure to CDFs may occur. For example, the level of CDFs in the blood of workers in the saw mill industry (exposure to 2,3,4,6-tetrachlorophenolate), textile industry (PCP exposure during fabric impregnation), and leather industry (PCP exposure during tanning) were measured, and the pattern of CDFs in the blood of exposed workers correlated with the CDFs in the exposed compounds (Rappe and Buser 1981). The intake from dermal exposure to CDD/CDF for workers in pulp mill (exposing hands in wet pulp) can be ≤7 pg TE/day (Kelada 1990). The concentrations of CDFs in adipose tissues of workers of a chemical plant (producing chlorophenols and 2,4,5-trichlorophenol among other chemicals) was much higher than those of a control population (Beck et al. 1989). Small but significantly ($p<0.05$) higher levels of 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF were found in lipid-adjusted serum of workers in a pesticide plant (2,4,5-trichlorophenol or its derivatives) compared to the levels in a control group (Piacitelli et al. 1992). Occupational exposure to CDFs may also occur in factories manufacturing and repairing transformers and capacitors, in factories with heat exchange systems containing PCBs, in factories using casting waxes containing PCBs or in industrial incinerators where materials containing chlorinated phenols, PCBs, and PCB ethers are incinerated (Rappe et al. 1979). The concentrations of CDDs/CDFs expressed as 2,3,7,8-tetraCDD TE in air of a municipal incinerator and an electrical transformer metal reclamation plant were significantly higher than ambient levels for these compounds (Crandall et al. 1992). However, no significant risk of exposure to tetraCDFs was found in modem resource recovery plants in Bristol, Connecticut, and Hillsborough County, Florida (Hahn et al. 1989).

Numerous data are available regarding the levels of CDFs in body tissue and fluids of exposed and background (no obvious source of exposure) population (Nagayama et al. 1977; Ryan 1986; Schecter et al. 1987; Tiernan et al. 1984; Young 1984). CDFs are lipophilic and tend to concentrate in fatty tissues. A positive correlation between 2,3,4,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 2,3,4,6,7,8-hexaCDF in adipose tissue and age of donor (higher concentrations at older age) was found (Le Be1 et al. 1990).

A similar correlation between 1,2,3,4,7,8-/ 1,2,3,6,7,8-hexaCDF and age of donor was also reported among the urban population in California (Stanley et al. 1989). No significant correlation between either the level of 2,3,7,8-tetraCDF, 1,2,3,4,6,7,8-heptaCDF, and octaCDF in adipose tissue and age of donor or between any CDFs and sex was discernable (Le Be1 et al. 1990). The latter findings are different from the case of 2,3,7,8-tetraCDD where higher concentrations of 2,3,7,8-tetraCDD were detected in female donors than male donors and a positive correlation between 2,3,7,8-tetraCDD levels and age of donors was found (Patterson et al. 1986). The average levels of 2,3,7,8-substituted CDFs in human fat of exposed and background populations of different countries have been reviewed (Jensen 1987). More recent data for the background levels of 2,3,7,8-substituted CDFs in human adipose tissues from different countries are given in Table 5-5. A comparative study of CDF contents in liver and adipose tissue of control humans (Germany) showed that on a fat basis, the concentrations of CDFs were higher in the liver than in adipose tissue (Beck et al. 1990; Thoma et al. 1990).

Several studies indicate that the levels of CDFs in the adipose tissue of exposed populations exceeds the levels detected in background or control populations. For example, adipose tissue levels of CDFs in an exposed patient of the Binghamton State Office Building (Schecter et al. 1985a, 1985c, 1986; Schecter and Ryan 1989), Yusho victims in Japan (Miyata et al. 1989; Ryan et al. 1987a), and three patients with fatal PCP poisoning (Ryan et al. 1987b) are all higher than control populations. However, no conclusive evidence of higher CDF exposure was found in seven people exposed during the Missouri dioxin episode and in Vietnam veterans (Kang et al. 1991; Needham et al. 1987). Certain municipal incinerator workers, such as those engaged in ash cleaning are exposed to higher levels of CDFs. The whole blood level of total CDFs in pooled blood of 56 such workers was 102.8 ppt (on lipid basis) compared to 47.0 ppt in pooled blood of 14 control subjects (Schecter et al. 1991c). The concentrations of 2,3,7,8-tetraCDF, 1,2,3,7,8-pentaCDF, 1,2,3,4,7,8-hexaCDF, 1,2,3,7,8,9-hexaCDF, 2,3,4,6,7,8-hexaCDF, 1,2,3,4,7,8,9-heptaCDF, and octaCDF were also higher in the pooled blood of workers compared to pooled blood of control subjects. No information on CDF levels in the tissues of sport fishermen or subsistence fishermen in the United States is available (Kimbrough 1991), although the levels of 1,2,3,4,7,8-hexaCDF and 1,2,3,4,6,7,8-heptaCDF in the serum lipids of people in Baltic regions who eat fish regularly was higher than those of a control population (Svensson et al. (1991). The estimated bioconcentration factor for 2,3,7,8-tetraCDF in human fat (on lipid basis) was 591 and was higher than other chlorinated aromatics including PCBs, octachlorostyrene, OCDD, and octaCDF (Geyer et al. 1987).

TABLE 5-5. Levels of CDFs in Human Adipose Tissue

Congener	Sample source and mean concentrations (ppt on fat basis)				
	Japan[a]	Sweden[a]	Germany[a]	Canada[b]	United States[c]
2,3,7,8-tetraCDF	9	3.9	0.9	3.3	9.1[d]
2,3,4,7,8-pentaCDF	25	54	44	33.3	40.0[e]
1,2,3,4,7,8-hexaCDF	15	6	10	37[f]	9.3
1,2,3,6,7,8-hexaCDF	14	5	6.7		5.4
2,3,4,6,7,8-hexaCDF	8	2	3.8	5.2	1.8
1,2,3,4,6,7,8-heptaCDF	No data	11	19.5	37.1	21.0[e]
octaCDF	No data	4	<1	12.0	60.0[d]

[a]Rappe et al. 1987
[b]Lebel et al. 1990
[c]Derived from Rappe 1989, unless otherwise stated
[d]Stanley et al. 1986
[e]EPA 1989
[f]These isomers were not separated

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A large number of data is available on the levels of CDFs in human milk from different countries (Dewailly et al. 1991; Schecter and Gasiewicz 1987a, 1987b; Schecter et al. 1989b). In general, CDF levels seem to be lower in the less industrialized countries than in more industrialized countries. Certain differences in specific isomers may exist in different countries, reflecting sources of contamination (Schecter et al. 1989d). The levels of CDFs in human milk derived from different countries are shown in Table 5-6. Levels of CDFs in human milk from other countries including South and North Vietnam and the former Soviet Union are also available (Schecter et al. 1989d, 1990c). From these data, it appears that the most prevalent congener in human milk is 2,3,4,7,8-pentaCDF, followed by 1,2,3,4,7,8-hexaCDF. In one study, no correlation was found between consumption of contaminated fish and accumulation of CDFs in the milk from nursing mothers (Hayward et al. 1989). During the breast feeding period, the level of CDFs in milk lipid-is . highest in the first week and slowly decreases thereafter (Beck et al. 1992; Fürst et al. 1989b). The level of CDFs in breast milk is highest for women having their first child and distinctly lower for women having their second and third child (Beck et al. 1992).

The levels of CDFs in human whole blood from various countries are listed in Table 5-7. Plasma levels of CDFs in people from different countries have been measured and the individual congener concentrations on a fat basis in control populations (not exposed to obvious sources of CDFs) vary from a minimum of <0.1 ppt for 2,3,7,8-tetraCDF to a maximum of 80 ppt for 2,3,4,7,8-pentaCDF (Chang et al. 1990; Nygren et al. 1988; Rappe 1991; Schecter 1991). The highest 2,3,4,7,8-pentaCDF concentration was found in a high fish-consuming population around the Baltic Sea (Svensson et al. 1991). The most prevalent congener in human plasma lipids in the United States was 1,2,3,4,6,7,8-heptaCDF, followed by 1,2,3,7,8- and 2,3,4,7,8-pentaCDF. This pattern was reversed in the plasma lipids of Swedish people where 2,3,4,7,8-pentaCDF was the prevalent congener followed by 1,2,3,4,6,7,8-heptaCDF (Chang et al. 1990). A similar pattern of high 2,3,4,7,8-pentaCDF level in blood was observed in human blood from Germany (Schecter et al. 1991b). Using a multivariate analysis, the concentration of CDFs in the plasma of exposed Vietnam veterans from the United States were determined to be slightly higher than matched controls (Nygren et al. 1988). It was also determined that higher chlorinated CDFs do not appear to partition according to the lipid content of whole blood. As the degree of chlorination increases, the percent associated with the protein fraction also increases. Therefore, it was concluded that partitioning of higher chlorinated CDFs is not dependent on lipid content, but specific binding to the protein fraction of serum and whole blood (Patterson et al. 1989; Schecter et al. 1991a).

TABLE 5-6. Levels of CDFs in Human Milk

Congener	Sample source and mean concentration (ppt on fat basis)			
	Sweden[a]	West Germany[b]	United States[c]	Japan[d]
2,3,7,8-tetraCDF	4.2	1.7	2.85	2.9
1,2,3,7,8-pentaCDF	<1.0	0.5	0.45	1.8
2,3,4,7,8-pentaCDF	21.3	26.7	7.3	23.0
1,2,3,4,7,8-hexaCDF	4.7	7.8	5.55	3.9
1,2,3,6,7,8-hexaCDF	3.4	6.5	3.2	2.5
2,3,4,6,7,8-hexaCDF	1.4	3.4	1.85	1.9
1,2,3,4,6,7,8-heptaCDF	7.4	5.5	4.05	3.3
octaCDF	3.2	1.4	4.1	<2.0

[a]Rappe 1987
[b]Fürst et al. 1992
[c]Schecter et al. 1991
[d]Rappe 1992

TABLE 5-7. Mean Levels of CDFs in Human Whole Blood (ppt Lipid) From Various Countries[a]

Congener	Germany		USA	Vietnam		
	N=85	Standard deviation	n=100[b]	Ho Chi Minh City N=50[b]	Dong Nai N=33[b]	Hanoi N=32[b]
2,3,7,8-tetraCDF	2.5	1.8	3.1	4.6	3.9	2.6
1,2,3,7,8-pentaCDF	Not detected		2.8	3.2	2.9	<1.1
2,3,4,7,8-pentaCDF	36.8	16.8	13.0	21	22	8.6
total pentaCDF	36.8		15.8	24.2	24.9	9.2
1,2,3,4,7,8-hexaCDF	17.5[c]		15.0	14.0	27.0	6.5
1,2,3,6,7,8-hexaCDF	13.7[c]		14.0	11.0	27.0	6.4
1,2,3,7,8,9-hexaCDF	Not detected[c]		Not detected (1.2)[d]	Not detected (1.4)[d]	Not detected (1.2)[d]	Not detected (1.1)[d]
2,3,4,6,7,8-hexaCDF	Not detected[c]		3.6	3.3	5	1.8
total hexaCDF	32.1[c]	20.8	32.6	28.3	59	14.7
1,2,3,4,6,7,8-heptaCDF	23.8[c]		36.0	22	31	12
1,2,3,4,7,8,9-heptaCDF	Not detected[c]		Not detected (1.8)[d]	2.6	2.7	<1.2
total hepta-CDF	24.1[c]	12.0	36.0	24.6	33.7	12.6
octaCDF	5.5	3.5	4.2	Not detected (5.5)[d]	11.0	<3.0

[a]Schecter 1991
[b]These samples were pooled into one.
[c]These values are derived from Päpke et al. 1989.
[d]The values in the parenthesis are the detection limits.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in industries that manufacture or use chemicals contaminated with CDFs are one segment of the population at high risk for CDF exposure (see Section 5.5). Among the general population, especially in more industrial countries, higher exposures to CDFs may occur among populations that consume high amounts of fatty fish contaminated with high levels of CDFs. This conclusion is based on a study of plasma CDF levels in fishermen and workers in the fish industry in Sweden (Svensson et al. 1991). However, the clinical significance of such exposures remains uncertain. Some emergency situations, such as accidental malfunction, fires, and explosions involving PCB capacitors and transformers may entail high exposures to CDFs (see section 5.4) (Vainio et a. 1989). Several 2,3,7,8-substituted CDFs are present in human milk at concentrations much higher than those in cow milk (Vainio et al. 1989). Therefore, consumption of human milk containing high levels of CDFs may pose a risk to infants consuming breast milk (Schecter and Gasiewicz 1987a, 1987b). Because of the relatively short period of intake and the accepted benefits of breastfeeding, the World Health Organization did not recommend limitations on breastfeeding (Vainio et al. 1989). Another population group that may be exposed to higher concentrations of CDFs includes people who live adjacent to uncontrolled landfill sites with soils containing high concentrations of CDFs (see Section 5.2). However, data correlating the levels of CDFs in body tissues or fluids (e.g., blood) with levels of exposure among this population group was not located.

5.7 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 CDFs 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 CDFs.

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.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The synthesis and purification of a specific CDF congener is a difficult task. The low water solubilities and vapor pressures contribute to the difficulty in determining the basic physico-chemical properties of the CDFs. In addition, the toxicity of some of the compounds requires extra care in their handling. Consequently, experimental data regarding the fundamental physical and chemical properties, such as melting point, boiling point, vapor pressure, and chemical reactivity for most of the CDF congeners remain unknown (see Table 3-2). Determination of experimental data on water solubility, K_{OW}, Henry's law constant, and K_{OC}, particularly for the 2,3,7,8-substituted CDFs (because of higher toxicity) would be useful for predicting the environmental fates and transport of these compounds.

Production, Import/Export, Use, Release, and Disposal. CDFs are produced on a small scale for chemical and biological laboratory use. These compounds have no other known use. Therefore, further development of data on the production, import/export, and use of these compounds would not be useful. The release of CDFs in the environment is one of the most intensively studied subjects in the literature (see Section 5.2). The regulations governing the disposal of CDF-containing wastes are well defined (see Section 4.4). However, it would be helpful to develop alternative methods of waste disposal that would not require treating the wastes at high temperatures or with harsh chemicals. Development of a biological degradation process capable of efficiently decontaminating CDF wastes within reasonable time would be useful.

Environmental Fate. The understanding of the environmental fate and transport of CDF has made major strides in the past few years (Atkinson 1991; Koester and Hites 1992). The estimated lifetimes of CDFs in air are such (see Section 5.3.2) that they will transport long distances in the air. Sediment will be the ultimate sink for CDFs present in air and water (Czuczwa and Hites 1986b). However, it would be helpful to develop more data on the photodegradability of CDFs present in the vapor phase in the air and in the adsorbed state as they are naturally present in water. The development of additional data regarding the biodegradability of these compounds in soil would also be useful.

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Bioavailability from Environmental Media. No data were located in the literature that either determine or estimate the bioavailability of CDFs from air, water, or soil as a result of inhalation of air, ingestion of water or soil, or dermal contact with soil. However, it is known that the CDFs would be present predominantly in the particulate phase in the air (Hites 1990), and in the adsorbed states in water and soil (Carsch et al. 1986; Czuczwa and Hites 1986b). Because of the strong adsorption of CDFs in soil, the bioavailability of these compounds due to dermal contact with soil is expected to be low. Since CDFs are present predominantly in the particulate-sorbed state in both air and in water, the bioavailability of CDFs from these media, as a result of inhalation exposure and ingestion of drinking water or soil, would be lower than the bioavailability of the compounds in the unadsorbed states (e.g., administered in solution or vapor form).

Food Chain Bioaccumulation. CDDs are bioconcentrated in aquatic organisms and in marine and terrestrial animals, but the magnitude of bioconcentration is lower than expected from predictive methods (e.g., K_{OW},). This is due to the fact that, at least some of these compounds are metabolized in aquatic organisms and animals (Frank and Schrap 1990; Norstrom et al. 1990; Opperhuizen and Sijm 1990). It would be helpful to develop a method that would circumvent the principal difficulty in determining the bioconcentration factors in aquatic organisms, that is, to develop a method for determining low concentrations of CDFs present in the solution phase in water (as opposed to the adsorbed state in particles in water). Development of more data regarding biomagnification of CDFs from lower trophic to higher trophic animals would also be useful. It would be useful to develop data on the biotransfer ratio of CDFs from soils to different plants.

Exposure Levels in Environmental Media. Data on the levels of CDFs in air, water, soil, sediment, and vegetation have been extensively developed (see Section 5.4). There is a paucity of data on the level of CDFs in drinking water. More comprehensive data on the levels of CDFs in the air and water of people who live near CDF-containing hazardous waste sites would be desirable. It would also be useful to develop data on typical daily intake of CDFs for a person in the United States due to inhalation of ambient air, and ingestion of drinking water and particularly food.

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

Exposure Levels in Humans. The levels of CDFs in tissues and body fluids of both exposed and control population groups in the United States have been extensively studied (see Section 5.4.4). However, more data on the levels of CDFs in body fluids and tissues of specific groups from the general population, such as those living near hazardous waste sites containing CDFs or those eating large amounts of fish, would be useful. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for CDFs were located. These substance are not currently on a subregistry of the National Exposure Registry. These substances will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to a substance.

5.7.2 On-going Studies

A study sponsored by the U.S. Department of Agriculture is being conducted by B. Eitzer in Connecticut to determine the levels and sources of CDFs in Housatonic River sediments (FEDRIP 1992).

Dr. Miller of the University of Nevada is conducting a study to determine the chemical and biochemical processes that affect the persistence of CDFs and their transformation products in plants, animals, and other environmental compartments (FEDRIP 1992).

A study is being conducted by the Arkansas Department of Health in collaboration with ATSDR/Division of Health Studies to determine whether people living near an incineration site are exposed to higher than background concentrations of CDFs and related compounds. It will study whether statistically significant higher levels of 2,3,7,8-substituted CDDs and CDFs are found in blood of residents compared with levels in the background population.

Other studies include investigations being conducted by Dr. A. Schecter (Clinical Campus of State University of New York (SUNY) Health Science Center in Binghamton, New York) on the levels of CDFs in human tissue and environmental samples from South and North Vietnam. Dr. Schecter is also conducting investigations in Russia to determine population exposure to CDFs due to a paper and

pulp mill in a remote part of Russia and occupational exposure to CDFs in another part of Russia. He is also conducting a serial tissue analysis of an occupationally exposed worker in Binghamton, New York, to determine the rate of decrease of several CDF congeners (Schecter 1992).

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 CDFs, its metabolites, and other biomarkers of exposure and effect to CDFs. 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 MATERIALS

Some of the methods used to analyze CDFs in biological samples are shown in Table 6-l. These methods are sufficiently sensitive to determine CDF levels in important biological tissues and body fluids. Besides these methods, the International Agency for Research on Cancer (IARC) has published several methods for the determination of CDFs in a variety of biological matrices (Norstrom and Simon 1991; Patterson et al. 1991; Ryan 1991a; Turner et al. 1991). The biological samples used for the determination of CDFs usually contain trace quantities of these compounds in a large matrix of the tissue or fluids. Other contaminants are usually present in biological matrices at much higher concentrations than CDFs, and some of the chlorinated aromatic contaminants are difficult to separate from CDFs. For these reasons, biological samples are subjected to extensive clean up procedures before quantitation. Since the use of high resolution gas chromatography (HRGC) provides an additional useful separation and mass spectrometry (MS) provides the most unambiguous identification, HRGC-MS is the preferred, or even exclusive method for the quantitation of CDFs (see Table 6-l). Sometimes, HRGC with electron capture detection is used for screening CDFs in samples, but quantitation is usually performed by MS. The use of high resolution is preferred over low resolution MS, because the high resolution provides more definitive identification and a lower limit of detection, Negative chemical ionization (NCI)-MS is preferable over electron impact mass

TABLE 6-1. Analytical Methods for Determining CDFs in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human serum	Sample labeled with ^{13}C-CDF containing 2,3,7,8-substituted congeners fractionated into lipo-protein, chylomicrons and red blood cells by centrifugation/ultracentrifugation, extract with $(NH_4)_2SO_4$, ethanol, and hexane; clean hexane layer with concentrated H_2SO_4, concentrate, and cleanup by column chromatography	HRGC/HRMS	5 ppq (pg/kg)	89–103.5	Patterson et al. 1989, 1987 (CDC method)
Human plasma	Spike plasma with ^{13}C-CDF and mix with formic acid and degas under vacuum, cleanup by reversed phase C-18 column, H_2SO_4 and multiple adsorbent column chromatography	HRGC/NCI-MS	No data	66–87	Chang et al. 1990
Human plasma/ adipose tissue	Extract sample with added ^{13}C-surrogate and internal standards with methanol and chloroform, separate chloroform layer by adding more chloroform, concentrate, and cleanup by multiple column chromatographic steps	HRGC/HRMS	0.003–0.02 ppt	64–135	Nygren et al. 1988
Human adipose tissue	Spike sample with ^{13}C-CDF, extract with methylene chloride, concentrate, cleanup by multiple column chromatography, add internal quantitation standard	HRGC/MS	2–10 ppt	No data	Stanley et al. 1986

TABLE 6-1. Analytical Methods for Determining CDFs in Biological Materials (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human adipose tissue	Spike tissue with isotopically labeled compounds, digest in concentrated HCl, extract with hexane, cleanup and fractionate by multiple column chromatography	HRGC/MS	1–10 ppt	No data	Graham et al. 1986
Human adipose tissue	Spike tissue with ^{13}C-CDF congeners and internal standard, extract with acetone/hexane, redissolve in dichloro-methane/cyclohexane, cleanup by gel permeation chromatography, further cleanup by multiple column chromatography	HRGC/HRGC	1 ppt	65.5–180.3 at 20 ppt	Le Bel et al. 1990
Human adipose and other tissues (adrenal, bone marrow, liver, muscle, spleen, kidney, and lung)	Homogenize tissue, extract with acetone/ hexane, spike with ^{37}Cl-CDF, cleanup with H_2SO_4 and multiple column chromatography	HRGC/MS	2 ppt	No data	Ryan et al. 1986, 1987b
Tissues (adipose, whole blood, serum, or organ section)	Spike tissue with ^{13}C-CDF internal standard, digest/extract with (1) HCl/ hexane in ultrasonic bath, or (2) potassium hydroxide/ethanol and extract with hexane, or (3) hexane/acetone in shaker; cleanup with concentrated H_2SO_4 and multiple column chromatography	HRGC/MS or HRGC/HRMS	2–25 ppt (for 2,3,7,8-tetraC DD)	50–90 (for 2,3,7,8-tetraCDD)	Tiernan et al. 1984

TABLE 6-1. Analytical Methods for Determining CDFs in Biological Materials (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Liver (rat, guinea pig, hamster, mouse)	Homogenize sample with sodium sulfate and ^{13}C-CDF internal standard, extra/ cleanup in a column of multiple adsorbents with cyclohexane-methylene chloride; further cleanup by column chromatography	HRGC/HRMS	0.1–1.0 ppt	55–110 ppt	Lindstroem and Rappe 1990
Egg yolk (OCDF only)	Homogenize with acetone-hexane, extract hexane, concentrate and cleanup by Biobeads S-X-3 column	Megabore GC/EDC (ASTM STP1075)	0.5–1.0 ppt lipid	53–120	Draper et al. 1991
Chicken egg and chicken liver	Homogenize sample with acetonitrile, add ^{13}C-CDF, separate acetonitrile layer, concentrate, and cleanup by reverse phase C-18 column; cleanup further with H_2SO_4 and multiple adsorbent column chromatography	HRGC/NCI-MS	No data	64–80	Chang et al. 1990
Cow milk	Spike sample with ^{13}C-tetraCDF, add acetone, extract with hexane, cleanup by multi-column chromatography and concentrated H_2SO_4 and further column and HPLC	HRGC/HRMS	0.01–0.7 ppt	47.3–57.9	Glidden et al. 1990

TABLE 6-1. Analytical Methods for Determining CDFs in Biological Materials (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human milk	Spike sample with internal standard, mix with formic acid and Lipidex 5000; wash mixture with methanol and elute into acetonitrile, cleanup by multiphase column chromatography	HRGC/MS	No data	64–100	Noren and Sjovall 1987

CDF = chlorinated dibenzofuran; H_2SO_4 = sulfuric acid; HCl = hydrochloric acid; HPLC = high performance liquid chromatography; HRGC = high resolution gas chromatography; HRMS = high resolution mass spectrometry; MS = mass spectrometry; $(NH_4)_2SO_4$ = ammonium sulfate; NCI-MS = negative chemical ionization mass spectrometry; tetraCDD = tetrachlorodibenzo-*p*-dioxin; tetraCDF = tetrachlorodibenzofuran

spectrometry (EI-MS) because the sensitivity of the negative chemical ionization is orders of magnitude better than EI-MS (Buser et al. 1985).

Since the concentrations of CDFs in most baseline biological samples are very low, extreme care must be used to ensure that all the reagents and equipments used during the analysis are scrupulously free of contamination. Glass bottles sealed with screw caps can be a source of contamination (Fürst et al. 1989). Owing to their lipophilic nature, CDFs in biological samples are largely associated with the lipid fraction. Procedures commonly used to eliminate lipid interference are saponification, concentrated sulfuric acid treatment, gel permeation chromatography, and column chromatography with suitable adsorbents (Chang et al. 1990). Saponification with hot ethanolic alkali has been shown to degrade higher chlorinated CDFs into lower chlorinated CDFs and ethoxy-CDFs as artifacts (Ryan et al. 1989). Because of the variability in the per cent lipid determination by different laboratories, it is advisable to take this into account when comparing CDF levels in blood and breast milk from different laboratories (Patterson et al. 1989b).

Because CDFs are usually present in biological samples in trace quantities, the more acceptable methods of analysis use internal standards to monitor method performance and quantitation purpose. Normally, ^{13}C- or ^{37}Cl-labeled CDFs are used as internal and recovery standard. In the absence of standard reference materials, the best method to ensure the reliability of quantitation is interlaboratory study (Albro et al. 1985). The quality assurance/quality control procedures used for the determination of CDFs in biological and environmental samples have been discussed (Mitchum and Donnelly 1991). A good review of different methods to analyze biological samples is available (Firestone 1991). An automated method has been proposed to reduce the labor intensive aspects of CDF analysis (Bicking and Wilson 1991).

6.2 ENVIRONMENTAL SAMPLES

Some of the methods used to determine CDF levels in environmental samples are shown in Table 6-2. Besides these methods, IARC has published several methods for the determination of CDFs in a variety of environmental samples (Luksemburg 1991; Ryan 1991b; Smith et al. 1991; Tondeur and Becker-t 1991; Tondeur et al. 1991). Other methods, including monoclonal antibodies for the immunoassay of CDFs (Stanker et al. 1987; Vanderlaan et al. 1988) and radioimmuno assay for 2,3,7,8-tetraCDF, are also available (Luster et al. 1980). Generally, the sensitivity of immunoassay

TABLE 6-2. Analytical Methods for Determining CDFs in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Ambient air	Spike sample collected on polyurethane foam/XAD-2 cartridge with a ^{37}Cl-CDF internal standard, extract with toluene, wash with acid and base, cleanup by multisection and multicolumn chromatography	HRGC/MS	0.01 pg/m^3	38-109 (for field samples)	Wagel et al. 1989
Ambient air	Spike sample collected on quartz fiber filter and polyurethane foam with ^{13}C-CDFs internal standard; Soxhlet extract with benzene; cleanup by acid-base separation and multicolumn chromatography on silica gel, alumina, and carbon	HRGC/HRMS	0.02–0.2 pg/m^3	74–98% at 0.2 ng spike	Harless et al. 1992
Ambient air	Spike sample collected on polyurethane foam/glass fiber filter with ^{13}C-CDFs internal standard, extract with acetone/ toluene, cleanup by multicolumn chromatography and HPLC	HRGC/NCI-MS	0.1–0.5 pg/m^3	88.3–113	Oehme et al. 1986
Stack gas effluent	Collect sample isokinetically with a modified EPA method 5 collection train, extract with benzene, spike with ^{13}C-tetraCDF internal standard, cleanup by 2-dimensional HPLC	HRGC-MS	No data	68–94	Nestrick and Lamparski 1989; Lamparski and Nestrick 1989

TABLE 6-2. Analytical Methods for Determining CDFs in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air, water, soil, sediment, ash, and fish	Spike sample with ^{13}C-CDF internal standard, extract (1) air filters, soil, sediment, and ash with toluene; (2) water with methylene chloride; and (3) fish with methylene chloride/cyclohexane; cleanup extract in multiphase column chromatography	HRGC/HRMS	No data	No data	Kleopfer et al. 1989
Precipitation (rain, snow)	Collect sample in a jug, pass collected water through XAD-2 cartridge with a glass fiber prefilter, spike cartridge with ^{13}C-CDF; extract cartridge with acetone-hexane and filter with toluene; cleanup by multilayer column chromatography and HPLC	HRGC/MS	1–7 ppq (for CDD)	42–86 (for CDD)	Tashiro et al. 1989
Water, soil, sludge, chemical wastes, fly ash	Spike sample with ^{13}C-CDFs, perform matrix-specific extraction, perform multicolumn cleanup, add recovery standard	HRGC/MS	0.63–2.53 ppt (reagent water) 0.11–0.83 ppb (soil) 0.06–0.30 ppb (fly ash) 0.46–2.17 ppb (sludge)	54.2–105.8	EPA 1986b (SW 846 [method 8280])

TABLE 6-2. Analytical Methods for Determining CDFs in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water, soil, sludge, chemical wastes, fly ash	Spike sample with ^{13}C-CDFs, perform matrix-specific extraction, cleanup by acid-base and multicolumn chromatography, add recovery standard	HRGC/HRMS	0.025–0.1 ppt (water) 2.5–12.5 ppt (soil and sediment) 2.5–12.5 ppt (fly ash) 12.5–62.5 ppt (sludge)	No data	Tondeur et al. 1989 (EPA method 8290)
Water, sludge	Pass river water and drinking water through a series of polyurethane foam; filter waste water through a spiked glass-fiber filter, and extract filtrate with methylene chloride; extract polyurethane foam, glass-fiber filter, and sludge with acetone/methylene chloride; concentrate all extracts, dissolve in hexane, cleanup by three column system	HRGC/HRMS	0.02 ppq (water) 0.3–18 ppt	No data	Rappe et al. 1989c
Soil	Spike sample with ^{13}C-CDF internal standard, extract with hexane/acetone, cleanup by multilayer and multicolumn, add recovery standard	HRGC/HRMS	No data	53–86	Creaser and Al-Haddad 1989
Soil (OCDF only)	Soxhlet extract sieved sample with hexane, concentrate and cleanup by Florisil®	Megabore GC/ECD (ASTM STP1075)	0.4–0.8 ng/g	101	Draper et al. 1991

TABLE 6-2. Analytical Methods for Determining CDFs in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fish, fish oil, soil, sediment	Spike sample with isotopic markers, homogenize with sodium sulfate, extract with selective solvent, cleanup by multilayer and multicolumn chromatography	HRGC/NCI-MS	<5 ppt	52–98 (for fish) 62–117 (for fish oil)	Smith et al. 1984
Canned meat	Spike sample with ^{13}C-tetraCDF, mix with sodium sulfate, extract with methylene chloride, cleanup by multilayer and multicolumn chromatography	HRGC/HRMS	16–39 ppq (pg/kg) (lipid wet basis)	70–120	LeFleur et al. 1990
Fish	Homogenize spiked sample, add concentrated HCl, extract with pentane, concentrate, cleanup by concentrated H_2SO_4 and multilayered, multicolumn chromatography	HRGC/MS	0.03–20 ppt	No data	Zacharewski et al. 1989
Fly ash	Extract sample with benzene, cleanup by HPLC fractionation	HRGC/MS (separation not isomer specific)	No data	No data	Tong et al. 1984
PCB, fly ash, and hexachlorophene	Dissolve or extract spiked (^{13}C-tetraCDF) with suitable solvent, separate by 2-dimensional gas chromatography	GC/GC/MS	No data	No data	Lignon and May 1986
Soot from PCB fire	Spike sample with ^{37}Cl-CDFs, saponify with alkali, extract with hexane, clean with H_2SO_4 and column chromatography	HRGC/HRMS	1–10 ppt	No data	Harless et al. 1983

TABLE 6-2. Analytical Methods for Determining CDFs in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Paper mill effluent, sludge	Spike sample with ^{13}C-tetraCDF, filter sample, extract filtrate with methylene chloride and residue or sludge with benzene/acetone; concentrate extract, cleanup with acid-base extraction, multicolumn chromatography	HRGC/HRMS	3.8 ppq (water) 0.34 ppq (solid sample)	40–65	Tiernan et al. 1989c
Polyethylene	Extract with decahydronaphthalene at 160°C, dilute with isooctane, filter; pan filtrate through activated basic alumina column and further cleanup by two stage HPLC fractionation	HRGC/MS	20–40 ppg (2,3,7,8-TCDF)	106% at 500 ppg	Nestrick et al. 1991
Paper products	Homogenize slurried sample, spike with ^{13}C-CDFs, extract with ethanol, cleanup by gel permeation chromatography, H_2SO_4 treatment and multicolumn chromatography	HRGC/HRMS	0.2–0.4 ppt	No data	Le Bel et al. 1991

CDD = chlorodibenzo-*p*-dioxin; CDF = chlorinated dibenzofuran; H_2SO_4 = sulfuric acid; HCl = hydrochloric acid; HPLC = high performance liquid chromatography; HRGC = high resolution gas chromatography; HRMS = high resolution mass spectrometry; MS = mass spectrometry; NCI-MS = negative chemical ionization mass spectrometry; tetraCDF = tetrachlorodibenzofuran

methods is lower than that attained by high resolution gas chromatography-high resolution mass spectrometry (see Table 6-2), and they require extensive cleanup. Induction bioassay analysis *is* also used for analysis of toxic CDFs in environmental samples. The 2,3,7,8-TCDD equivalents in chemically cleaned fish extracts were determined by their activities as inducers of AHH and EROD in rat hepatoma H-4-11 E cells in culture (Zacharewski et al. 1989). Analytical methods sensitive enough to determine the very low concentrations of CDFs present in most drinking waters are not yet available.

A review of analytical methods used to determine CDF levels in environmental samples is available (Buser 1991; Buser et al. 1985). A combination of glass fiber filters and polyurethane foam plugs is suitable for collecting airborne CDFs (Tashiro et al. 1989). Ultrasonic extraction has been recommended as the inexpensive, efficient, reliable, and rapid method for the extraction of CDFs from fly ash (Beard et al. 1992). The multiphase silica, acidic alumina, and AX-21 (a porous carbon) are very suitable for cleaning up environmental samples including interference from chlorinated diphenyl ethers (Donnelly et al. 1990; Huestis and Sergeant 1992). The relative retention times of all 87 CDF congeners containing 4 to 8 chlorine atoms on the commonly used capillary chromatographic columns have been determined (Ryan et al. 1991). A minimum of two columns are needed to separate all 87 congener peaks from each other. The capabilities of different mass spectral techniques for determining CDF levels in environmental samples have been compared, and the advantage of the MS/MS system over HRMS and LRMS (low resolution MS) have been discussed (Charles and Tondeur 1990; Marbury et al. 1992; McCurvin et al. 1989; Reiner et al. 1991). The advantages and disadvantages of negative ionization low resolution MS over HRGC have also been discussed (Koester et al. 1992). As in the case of biological samples, the results of CDF analysis from different laboratories should be compared to ensure that the data are reliable (Addis et al. 1989; Bradley et al. 1990; Liem et al. 1989).

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 CDFs 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 CDFs.

6. ANALYTICAL METHODS

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. The levels of CDFs in serum and plasma, human milk, and biological tissues are used as biomarkers of exposure to these compounds (Ryan et al. 1985b; Schecter and Ryan 1985) (see Section 2.5.1). Analytical methods for determining CDF levels in biological tissues and fluids are available that can distinguish the levels of these compounds in control versus exposed populations (see Section 5.4.4 and Table 6-l). Increased sensitivity in the method of determining CDFs in blood would be useful, since blood is the least invasive of the biomedia used as biomarkers of exposure.

No specific biomarkers of effects of CDFs in humans were located (see Section 2.5.2).

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods of sufficient sensitivity to determine CDF levels in most environmental media are available (see Table 6-2). However, the concentration of CDFs in drinking water is so low that suitable methods for determining the concentration are not available. However, the contribution of drinking water to the total intake of CDFs in humans is so low, there is no compelling need to develop analytical methods for the determination of CDFs in drinking water.

The compounds identified as photodegradation products of higher chlorinated CDFs are lower chlorinated CDFs. In fish, a hydroxylated CDF has been identified as a metabolite. Analytical methods capable of determining the photolytic products and hydroxylated compound in fish are available (Frank and Schrap 1990; Koshioka et al. 1987). Further development of methods from the determination of environmental degradation products of CDFs are not warranted.

6.3.2 On-going Studies

6. ANALYTICAL METHODS

As part of a larger project to determine human health hazards from exposure to PCBs and CDFs for people living near a dumpsite, investigators are developing new analytical methods to monitor congener-specific levels of these compounds in feces and urine. The summary of the proposed analytical method was not provided. This research is being conducted by a group headed by Dr. Carpenter of the State University of New York at Albany, New York (FEDRIP 1992). Dr. Tomer of the National Institute of Health is conducting a research project aimed at elucidating the structures and increasing the sensitivity of CDFs and their conjugates excreted by animals. The investigator is attempting to increase the sensitivity of CDF detection by hybrid MS/MS with a combination of high flux/low level sample introduction systems (FEDRIP 1992).

7. REGULATIONS AND ADVISORIES

ATSDR has derived an MRL of 0.001 μg/kg/day for acute-duration oral exposure to 2,3,4,7,8-pentaCDF based on a LOAEL for thymic effects in guinea pigs (Moore et al. 1979). ATSDR also has derived an MRL of 0.00003 μg/kg/day for intermediate-duration oral exposure to 2,3,4,7,8-pentaCDF based on a LOAEL for hepatic effects in rats (Pleuss et al. 1988a; Poiger et al. 1979). Because 2,3,4,7,8-pentaCDF is more toxic than some other CDF congeners, applying these MRLs to other CDFs may lead to overestimating actual risks.

International or state regulations and guidelines on human exposure to CDFs were not located. However, CDFs have been listed as hazardous waste constituents (EPA 1988).

Methodology for quantitatively assessing health risks of CDFs is currently being evaluated by ATSDR (see Section 2.9.2).

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9. GLOSSARY

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

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.

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.

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.

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.

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.

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 occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

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.

Henry's Law Constant (H) - The ratio of partial pressure of a solute above the solvent over the mole fraction of the solute in dilute solution under equilibrium conditions.

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

9. GLOSSARY

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

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 is expected 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 dose 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.

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

Minimal Risk Level - An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mixed Function Oxygenases (MFO) - A family of microsomal enzymes, located primarily in the liver, which is responsible for the metabolism of exogenous compounds by addition of a hydroxyl moiety to the foreign substrate.

Mutagen - A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity - The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) - The dose of 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.

Permissible Exposure Limit (PEL) - An allowable exposure level in workplace air averaged over an 8-hour shift.

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 $\mu g/m^3$ for air).

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 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 CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity - The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) - The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity - This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen - A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) - A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) - An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

9. GLOSSARY

Toxic Dose (TD_{50}) - A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) - A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people ,living in the vicinity of a hazardous waste site or substance 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 substance.

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 by duration of exposure and end point and to illustrate graphically levels of exposure associated with those effects. 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) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minima1 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. The LSE tables and figures can be used 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.

The legends presented- below demonstrate the application of these tables and figures. A representative example of LSE Table 2-l and Figure 2-1 are shown. The numbers in the left columrn 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 mute of exposure. When sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE 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.

2) Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

APPENDIX A

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.

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 define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

5) Species The test species, whether animal or human, are identified in this column.

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 [substance XI via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

7) System This column further defines the systemic effects. These systems include: respiratory9 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 nmber 18, one systemic effect (respiratory) was investigated in this study.

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 exposure level 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 "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

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 epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer9 but the text may report doses which did not cause a measurable increase in cancer.

12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables ate 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 LSE 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 levels for particular exposure duration.

TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer							
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

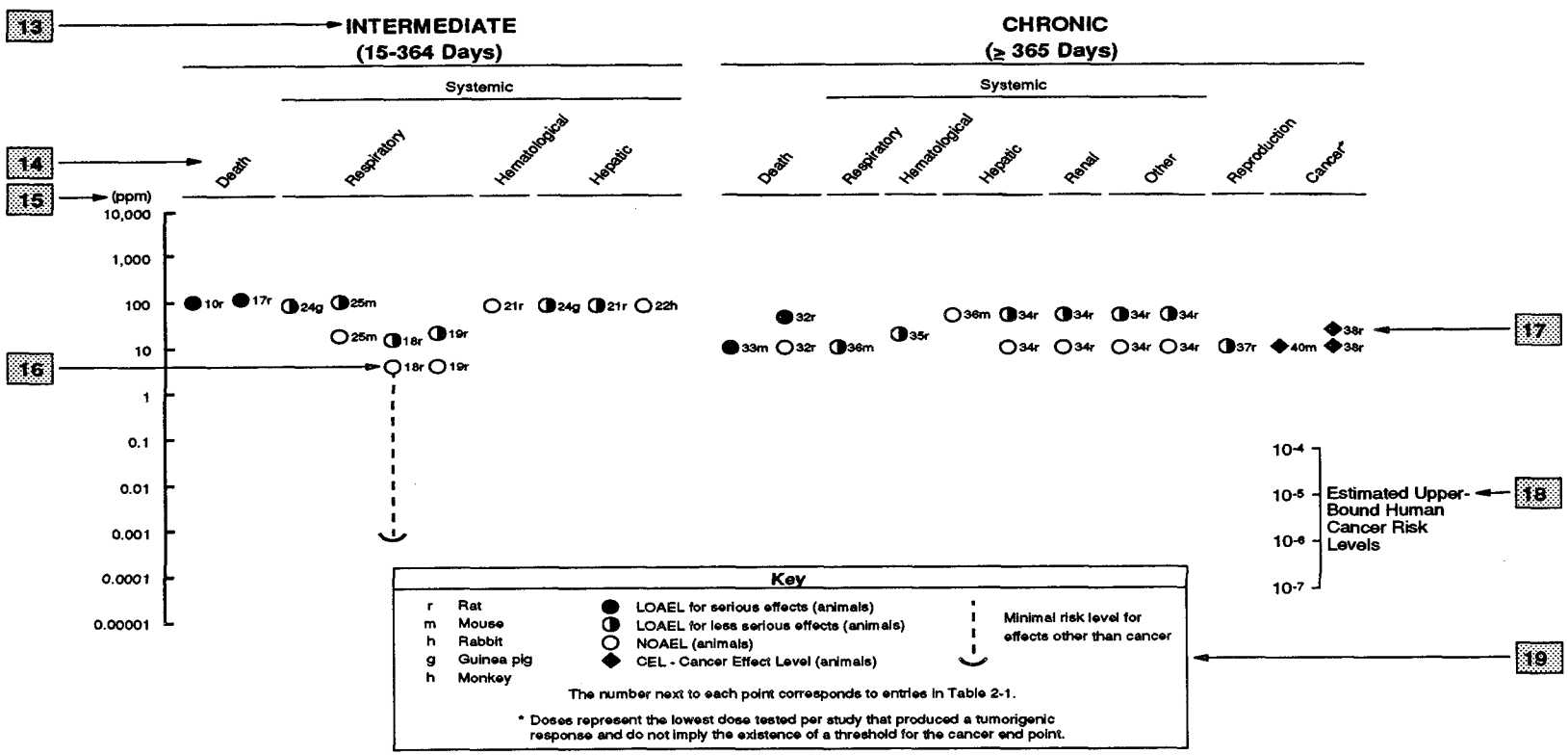
[a] The number corresponds to entries in Figure 2-1.

[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 = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

FIGURE 2-1. Levels of Significant Exposure to [Chemical X] - Inhalation



13) Exposure Duration 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 exist. The same health effects appear in the LSE table.

15) Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported 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, 1% 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 a NOAEL for the test species (rat). The key numbr 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 MRI, of 0.005 ppm (see footnote "b" in the LSE table).

17) CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). 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 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.

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological 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 discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and *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.

APPENDIX A

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. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - 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 substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Chemicals” and 2.7, “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 used by the Environmental Protection Agency (EPA) (Barnes and Dourson 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the 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 effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the 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. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor of (19 3, or 10) is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of (1, 3, or 10) are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and (1, 3, or 10) are used for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. Generally an uncertainty factor of 10 is used; however, the MRL Workgroup reserves the right to use uncertainty factors of (1, 3, or 10) based on scientific judgement. The product is then divided into the adjusted 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 B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MFO	mixed function oxygenases
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
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
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification

SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TEF	toxicity equivalency factor
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
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
δ	delta
γ	gamma
μm	micron
μg	microgram

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