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EPA

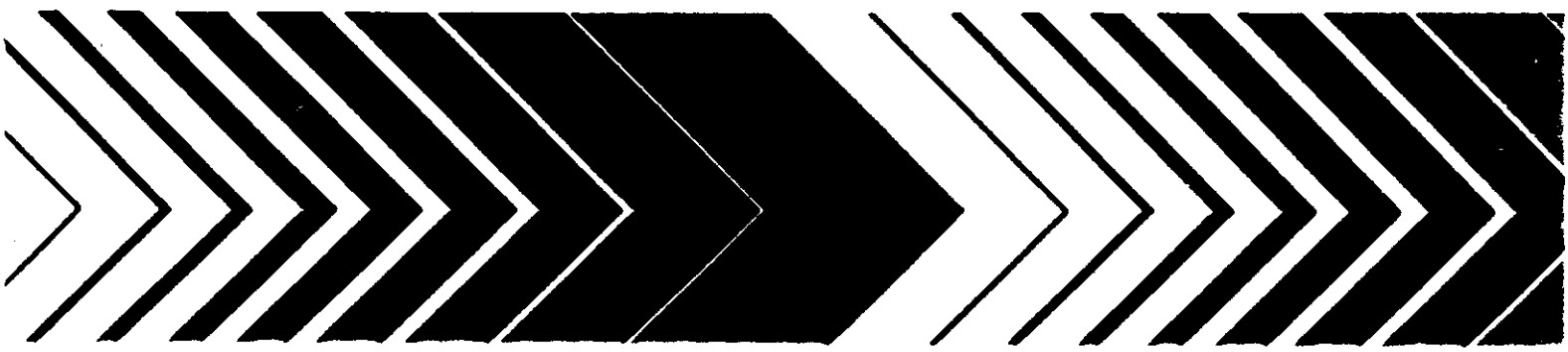
Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds

Review Draft (Do Not Cite or Quote)

Volume III of III

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.



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Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, D.C.

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Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Related Compounds

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LIST OF ABBREVIATIONS AND ACRONYMS

ACTH	Adrenocorticotrophic hormone
Ah receptor	Aryl hydrocarbon receptor
AHH	Aryl hydrocarbon hydroxylase
ALA	Aminolevulinic acid
ALT	L-alanine aminotransferase
AOR	Adjusted odds ratio
APC	Antigen-presenting cells
AST	L-aspartate aminotransferase
ATPase	Adenosine triphosphatase
BDD	Brominated dibenzo-*p*-dioxin
BDF	Brominated dibenzofuran
BCF	Bioconcentration factor
BGG	Bovine gamma globulin
bHLH	Basic helix-loop-helix
bw	Body weight
cAMP	Cyclic 3,5-adenosine monophosphate
CDC	Centers for Disease Control and Prevention
CDD	Chlorinated dibenzo-*p*-dioxin
CDF	Chlorinated dibenzofuran
cDNA	Complementary DNA
cl	Confidence level
CMI	Cornell Medical Index
CNS	Central nervous system
CSM	Cerebrospinal malformation
CTL	Cytotoxic T lymphocyte
DCDD	2,7-Dichlorodibenzo-*p*-dioxin

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

DEN	Diethylnitrosamine
DHT	5α-Dihydrotestosterone
DIS	Diagnostic Interview Schedule
DMBA	Dimethylbenzanthracene
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DRE	Dioxin-responsive enhancers
DTH	Delayed-type hypersensitivity
EC_{50}	Concentration effective for 50% of organisms tested
EC_{100}	Concentration effective for 100% of organisms tested
ED_{50}	Dose effective for 50% of recipients
ECOD	7-Ethoxycoumarin-O-deethylase
EEG	Electroencephalogram
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
EROD	7-Ethoxyresorufin-O-deethylase
EOF	Enzyme altered foci
EOI	Exposure opportunity index
FEV	Forced expiratory volume
FIQ	Full-scale IQ
FSH	Follicle-stimulating hormone
FTI	Free thyroxine index
FVC	Forced vital capacity
GC-ECD	Gas chromatograph-electron capture detection
GC/MS	Gas chromatograph/mass spectrometer

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

GGT	Gamma glutamyl transpeptidase
GnRH	Gonadotropin-releasing hormone
GST	Glutathione-S-transferase
GVH	Graft versus host
HAH	Halogenated aromatic hydrocarbons
HCB	Hexachlorobenzene
HCDD	Hexachlorodibenzo-*p*-dioxin
HDL	High density lipoprotein
HLH	Helix-loop-helix
HPAH	Halogenated polycyclic aromatic hydrocarbon
HpCDD	Heptachlorinated dibenzo-*p*-dioxin
HpCDF	Heptachlorinated dibenzofuran
HPLC	High performance liquid chromatography
HRB	Halstead-Reitan Battery
HRGC/HRMS	High resolution gas chromatography/high resolution mass spectrometry
HTL	Human tonsillar lymphocytes
HxBB	Hexabrom-biphenyl
HxCB	Hexachlorobiphenyl
HxCDD	Hexachlorinated dibenzo-*p*-dioxin
HxCDF	Hexachlorinated dibenzofuran
ICD-9	International Classification of Diseases 9
ID_{50}	Dose infective to 50% of recipients
I-TEF	International TCDD-toxic-equivalency
KVK	Kemisk Vaerk Køge
LADD	Lifetime average daily dose
LD_{50}	Dose lethal to 50% of recipients (and all other subscripter dose levels)

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

LDH	L-lactate dehydrogenase
LH	Luteinizing hormone
LDL	Low density liproprotein
LMS	Linearized multistage
LPL	Lipoprotein lipase activity
LOAEL	Lowest-observable-adverse-effect level
LOEL	Lowest-observed-effect level
LPS	Lipopolysaccharide
MACDP	Metropolitan Atlanta Congenital Defects Program
3-MC	3-Methylcholanthrene
MCDF	6-Methyl-1,3,8-trichlorodibenzofuran
MCF-7	(breast cancer cell)
MCMI	Millon Clinical Multiaxial Inventory
MCPA	(4-Chloro-2-methylphenoxy)acetic acid
MCPB	2-Methyl-4-chlorophenoxybutyric acid
MCPP	2-(4-Chloro-2-methylphenoxy)-propanoic acid
MFO	Mixed function oxidase
MMPI	Minnesota Multiphase Personality Inventory
MLE	Maximum likelihood estimate
mRNA	Messenger RNA
MNNG	*N*-methyl-*N*-nitrosoguanidine
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NaTCP	Sodium 2,4,5-trichlorophenate
NHL	Non-Hodgkin's lymphoma
NIEHS	National Institute of Environmental Health Sciences

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

NIOSH	National Institute for Occupational Safety and Health
NK	Natural killer
NOAEL	No-observable-adverse-effect level
NOEL	No-observed-effect level
NTP	National Toxicology Program
OCDD	Octachlorodibenzo-*p*-dioxin
OCDF	Octachlorodibenzofuran
OR	Odds ratio
OVX	Ovariectomized
PAA	Phenoxyacetic acid
PAH	Polyaromatic hydrocarbon
PBA	Phenoxybutyric acid
PBB	Polybrominated biphenyl
PBF	Percent body fat
PBL	Peripheral blood lymphocytes
PB-PK	Physiologically based pharmacokinetic
PCB	Polychlorinated biphenyl
PCBA	Phenoxybutyric acid
PCDD	Polychlorinated dibenzodioxin
PCDF	Polychlorinated dibenzofuran
PCP	Pentachlorophenol
PCPA	Parachlorophenoxyacetic acid
PCQ	Quaterphenyl
PCT	Porphyria cutanea tarda
PeCDD	Pentachlorinated dibenzo-*p*-dioxin
PeCDF	Pentachlorinated dibenzo-*p*-dioxin

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

PEPCK	Phosphoenol pyruvate carboxykinase
PFC	Plaque-forming cell
PGE_2	Prostaglandin E_2
$PGF_{2\alpha}$	Prostaglandin $F_{2\alpha}$
PGST	Placental glutathione-S-transferase
PGT	Placental glutathione transferase
PHA	Phytohemagglutinin
PIQ	Performance IQ
PKC	Protein kinase C
PNS	Peripheral nervous system
POMS	Profile of Mood States
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
PRR	Prevalence risk ratio
PWM	Pokeweed mitogen
RNA	Ribonucleic acid
RR	Relative risk
SAR	Structure-activity relationships
SB-IQ	Standford Binet IQ
SCL-90-R	Self-Report Symptom Checklist-90-Revised
SD	Standard deviation
SE	Standard error
SEA	Southeast Asia
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

SIR	Standard incidence ratio
SMR	Standardized mortality ratio
SRBC	Sheep erythrocytes (red blood cells)
STS	Soft tissue sarcoma
$t_{½}$	Half-time
TBB	Tetrabromobiphenyl
TBDD	Tetrabrominated dibenzo-*p*-dioxin
TBDF	Tetrabrominated dibenzo-*p*-furan
TBG	Thyroxine-binding globulin
TBP	Thyroxine-binding protein
TCAOB	Tetrachloroazoxybenzene
TCB	Tetrachlorobiphenyl
TCDD	Tetrachlorodibenzo-*p*-dioxin
TCDF	Tetrachlorodibenzofuran
TCP	Trichlorophenol
TEF	Toxic equivalency factors
TEQ	Toxic equivalents
TGF	Thyroid growth factor
TI	T helper cell independent
TNF	Tumor necrosis factor
tPA	Tissue plasminogen activator
TPA	Tetradecanoyl phorbol acetate
TSH	Thyroid-stimulating hormone
TT	Tetanus toxoid
TTR	Transthyretrin
TxB_2	Thromboxane B_2

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

UDP	Uridine diphosphate
UDPGT	UDP-glucuronosyltransferase
URO-D	Uroporphyrinogen decarboxylase
VIQ	Verbal IQ
VLDL	Very low density lipoprotein
v/v	Volume per volume
w/w	Weight by weight
WAIS	Wechsler Adult Intelligence Scale
WISC-R	Wechsler Intelligence Scale for Children, Revised

PREFACE

In April 1991, the U.S. Environmental Protection Agency (EPA) announced that it would conduct a scientific reassessment of the health risks of exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and chemically similar compounds collectively known as dioxin. The EPA has undertaken this task in response to emerging scientific knowledge of the biological, human health, and environmental effects of dioxin. Significant advances have occurred in the scientific understanding of mechanisms of dioxin toxicity, of the carcinogenic and other adverse health effects of dioxin in people, of the pathways to human exposure, and of the toxic effects of dioxin to the environment.

In 1985 and 1988, the Agency prepared assessments of the human health risks from environmental exposures to dioxin. Also, in 1988, a draft exposure document was prepared that presented procedures for conducting site-specific exposure assessments to dioxin-like compounds. These assessments were reviewed by the Agency's Science Advisory Board (SAB). At the time of the 1988 assessments, there was general agreement within the scientific community that there could be a substantial improvement over the existing approach to analyzing dose response, but there was no consensus as to a more biologically defensible methodology. The Agency was asked to explore the development of such a method. The current reassessment activities are in response to this request.

The scientific reassessment of dioxin consists of five activities:

1. Update and revision of the health assessment document for dioxin.
2. Laboratory research in support of the dose-response model.
3. Development of a biologically based dose-response model for dioxin.
4. Update and revision of the dioxin exposure assessment document.
5. Research to characterize ecological risks in aquatic ecosystems.

PREFACE (continued)

The first four activities have resulted in two draft documents (the health assessment document and exposure document) for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds. These companion documents, which form the basis for the Agency's reassessment of dioxin, have been used in the development of the risk characterization chapter that follows the health assessment. The process for developing these documents consisted of three phases which are outlined in later paragraphs.

The fifth activity, which is in progress at EPA's Environmental Research Laboratory in Duluth, Minnesota, involves characterizing ecological risks in aquatic ecosystems from exposure to dioxins. Research efforts are focused on the study of organisms in aquatic food webs to identify the effects of dioxin exposure that are likely to result in significant population impacts. A report titled, *Interim Report on Data and Methods for the Assessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) Risks to Aquatic Organisms and Associated Wildlife* (EPA/600/R-93/055), was published in April 1993. This report will serve as a background document for assessing dioxin-related ecological risks. Ultimately, these data will support the development of aquatic life criteria which will aid in the implementation of the Clean Water Act.

The EPA had endeavored to make each phase of the current reassessment of dioxin an open and participatory effort. On November 15, 1991, and April 28, 1992, public meetings were held to inform the public of the Agency's plans and activities for the reassessment, to hear and receive public comments and reviews of the proposed plans, and to receive any current, scientifically relevant information.

In the Fall of 1992, the Agency convened two peer-review workshops to review draft documents related to EPA's scientific reassessment of the health effects of dioxin. The first workshop was held September 10 and 11, 1992, to review a draft exposure assessment titled, *Estimating Exposures to Dioxin-Like Compounds*. The second workshop was held September 22-25, 1992, to review eight chapters of a future draft *Health*

PREFACE (continued)

Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds. Peer-reviewers were also asked to identify issues to be incorporated into the risk characterization, which was under development.

In the Fall of 1993, a third peer-review workshop was held on September 7 and 8, 1993, to review a draft of the revised and expanded Epidemiology and Human Data Chapter, which also would be part of the future health assessment document. The revised chapter provided an evaluation of the scientific quality and strength of the epidemiology data in the evaluation of toxic health effects, both cancer and noncancer, from exposure to dioxin, with an emphasis on the specific congener, 2,3,7,8-TCDD.

As mentioned previously, completion of the health assessment and exposure documents involves three phases: Phase 1 involved drafting state-of-the-science chapters and a dose-response model for the health assessment document, expanding the exposure document to address dioxin related compounds, and conducting peer review workshops by panels of experts. This phase has been completed.

Phase 2, preparation of the risk characterization, began during the September 1992 workshops with discussions by the peer-review panels and formulation of points to be carried forward into the risk characterization. Following the September 1993 workshop, this work was completed and was incorporated as Chapter 9 of the draft health assessment document. This phase has been completed.

Phase 3 is currently underway. It includes making External Review Drafts of both the health assessment document and the exposure document available for public review and comment.

Following the public comment period, the Agency's Science Advisory Board (SAB) will review the draft documents in public session. Assuming that public and SAB comments are positive, the draft documents will be revised, and final documents will be issued.

PREFACE (continued)

The *Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds* has been prepared under the direction of the Office of Health and Environmental Assessment, Office of Research and Development, which is responsible for the report's scientific accuracy and conclusions. A comprehensive search of the scientific literature for this document varies somewhat by chapter but is, in general, complete through January 1994.

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This draft Health Assessment Document was prepared under the leadership and direction of the Office of Health and Environmental Assessment (OHEA) within EPA's Office of Research and Development (ORD). The overall coordination and leadership of the activities associated with EPA's reassessment of dioxin, which includes the development of this draft document, is Dr. William H. Farland, Director of OHEA.

Authors and chapter managers for the Health Assessment Document are listed below. Early drafts of some chapters were prepared by Syracuse Research Corporation under EPA Contract No. 68-CO-0043. Other chapters were authored totally or in part by scientists within EPA and other agencies within the federal government. The ORD chapter managers were responsible for providing oversight, review, and technical editing of successive drafts, and incorporating comments from reviewers to develop a comprehensive and consistent document. In some cases, the chapter managers also authored sections or parts of the chapter.

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Early drafts of Chapters 1 through 8 of this health assessment were reviewed by a panel of experts at a peer-review workshop held September 22-25, 1992. Members of the Peer Review Panel for this workshop were as follows:

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On September 7 and 8, 1993, a peer-review workshop was held to review a greatly revised and expanded draft Chapter 7 (Epidemiology/ Human Data). Members of the Peer Review Panel for this workshop are as follows:

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In addition, during the development of this draft Health Assessment Document, selected sections, chapters, or volumes were peer reviewed by scientists and experts within EPA and other federal agencies, as well as by experts in academia and the private sector.

A draft of Chapter 9, the risk characterization, was reviewed by an interagency workgroup comprising scientists from the following agencies of the federal government:

Department of Agriculture

Department of Defense

Department of Health and Human Services*

*Drafts of Chapters 7 and 9 have been reviewed by the Subcommittee on Risk Assessment of the Committee to Coordinate Health and Environmental Related Programs (CCEHRP) under the direction of Bryan D. Hardin of the National Institute for Occupational Safety and Health, Centers for Disease Control, Department of Health and Human Services, and Ron Coene, Executive Secretary of CCEHRP.

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Department of Labor (Occupational Safety and Health Administration)

Department of Veterans Affairs

Executive Office of the President

- Office of Science and Technology Policy
- Council of Economic Advisors
- Domestic Policy Council

9. RISK CHARACTERIZATION OF DIOXIN AND RELATED COMPOUNDS

9.1. INTRODUCTION

Chlorinated dibenzo-*p*-dioxins and related compounds (commonly known simply as dioxins) are contaminants present in a variety of environmental media. This class of compounds has caused great concern in the general public as well as intense interest in the scientific community. Much of the public concern revolves around the characterization of these compounds as among the most potent "man-made" toxicants ever studied. Indeed, these compounds are extremely potent in producing a variety of effects in experimental animals based on traditional toxicology studies at levels hundreds or thousands of times lower than most chemicals of environmental interest. In addition, human studies demonstrate that exposure to dioxin and related compounds is associated with subtle biochemical and biological changes whose clinical significance is as yet unknown and with chloracne, a serious skin condition associated with these and similar organic chemicals. Laboratory studies suggest the probability that exposure to dioxin-like compounds may be associated with other serious health effects including cancer. Human data, while often limited in their ability to answer questions of hazard and risk, are generally consistent with the observations in animals. Whether the adverse effects noted above are expressed in humans, or are detectable in human population studies, is dependent on the dose absorbed and the intrinsic sensitivity of humans to these compounds. Recent laboratory studies have provided new insights into the mechanisms involved in the impact of dioxins on various cells and tissues and, ultimately, on toxicity. Dioxins have been demonstrated to be potent modulators of cellular growth and differentiation, particularly in epithelial tissues. These data, together with the collective body of information from animal and human studies, when coupled with assumptions and inferences regarding extrapolation from experimental animals to humans and from high doses to low doses, allow a characterization of dioxin hazards.

This chapter presents a risk characterization for dioxin and related compounds. In the risk characterization, key findings pertinent to understanding the hazards and risks of dioxin and related compounds are described and integrated. All of the available information is considered in proposing hypotheses or in reaching conclusions. The risk characterization is

not meant to be an executive summary of the extensive data base that has been analyzed in detail in preceding chapters and in the Exposure Document. Risk characterization requires a discussion of likely routes, patterns, and levels of exposure as well as aspects of hazard and dose response. Information contained in the document titled *Estimating Exposure to Dioxin-like Compounds* (U.S. EPA, 1994), hereafter referred to as the Exposure Document, will be integrated with the health effects information on this class of compounds found in previous chapters of this assessment. The risk characterization articulates the strengths and weaknesses of the available evidence and clearly presents assumptions made and inferences used. Risk is characterized in both qualitative and quantitative terms, as appropriate. Finally, overall conclusions regarding the health risks of dioxin and related compounds are presented.

The process for developing this risk characterization of dioxin and related compounds has been an open and participatory one. The Health Assessment and Exposure Documents that provide the basis for this characterization have been developed in collaboration with scientists from within and from outside of the Federal Government. Each of these has undergone extensive internal and external review, including review at a meeting of experts after a first draft was completed. Additional input to this characterization comes from comments on those draft chapters as well as from the panel of experts that met in September 1992. Panel members were asked to provide their perspective on themes to be carried into the characterization and their contributions are reflected here. Finally, the characterization, as presented here, reflects review and comment by both those Federal scientists involved in developing the health assessment and exposure chapters as well as representatives of other Federal agencies. However, the views expressed in this characterization are those of the collective authors and, as a draft undergoing public comment and further external review, no Agency-level endorsement should be inferred at this time.

Once fully peer reviewed and revised accordingly, this risk characterization is meant to provide a balanced picture of the scientific findings of the health and exposure assessments for use by risk managers in selecting risk management options, based on this and other information. As an integrated analysis of a complex data base, it is meant to answer key

questions concerning the science behind concerns for dioxins and should be useful in developing strategies for risk communication.

9.2. CHEMICAL STRUCTURE AND PROPERTIES

Polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) are chemically classified as halogenated aromatic hydrocarbons. The chlorinated and brominated dibenzodioxins and dibenzofurans are tricyclic aromatic compounds with similar physical and chemical properties, and both classes are similar structurally. Certain of the PCBs (the so-called coplanar or mono-ortho coplanar congeners) are also structurally and conformationally similar. The most widely studied of these compounds is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). This compound, often called simply dioxin, represents the reference compound for this class of compounds. The structure of TCDD and several related compounds is shown in Figure 9-1.

For purposes of this document, dioxin-like compounds are defined to include the subset of this class of compounds, which are generally agreed to produce dioxin-like toxicity. These compounds are assigned individual toxicity equivalence factor (TEF) values as defined by international convention (U.S. EPA, 1989). Results of in vitro and in vivo laboratory studies contribute to the assignment of a relative toxicity value. TEFs are estimates of the toxicity of dioxin-like compounds relative to the toxicity of TCDD, which is assigned a TEF of 1.0. All chlorinated dibenzodioxins (CDDs) and chlorinated dibenzofurans (CDFs) with chlorines substituted in the 2,3,7, and 8 positions are assigned TEF values. Additionally, the analogous brominated dioxins and furans (BDDs and BDFs) and certain polychlorinated biphenyls have recently been identified as having dioxin-like toxicity and thus are also included in the definition of dioxin-like compounds. Generally accepted TEF values for chlorinated dibenzodioxins and dibenzofurans are shown in Table 9-1. A recent World Health Organization/International Program on Chemical Safety meeting held in The Netherlands in December 1993 considered the need to derive internationally acceptable interim TEFs for the dioxin-like PCBs. Recommendations arising from that meeting of experts (Ahlborg et al., 1994) suggest that in general only a few of the dioxin-like PCBs are likely to be significant contributors to general population exposures to dioxin-like

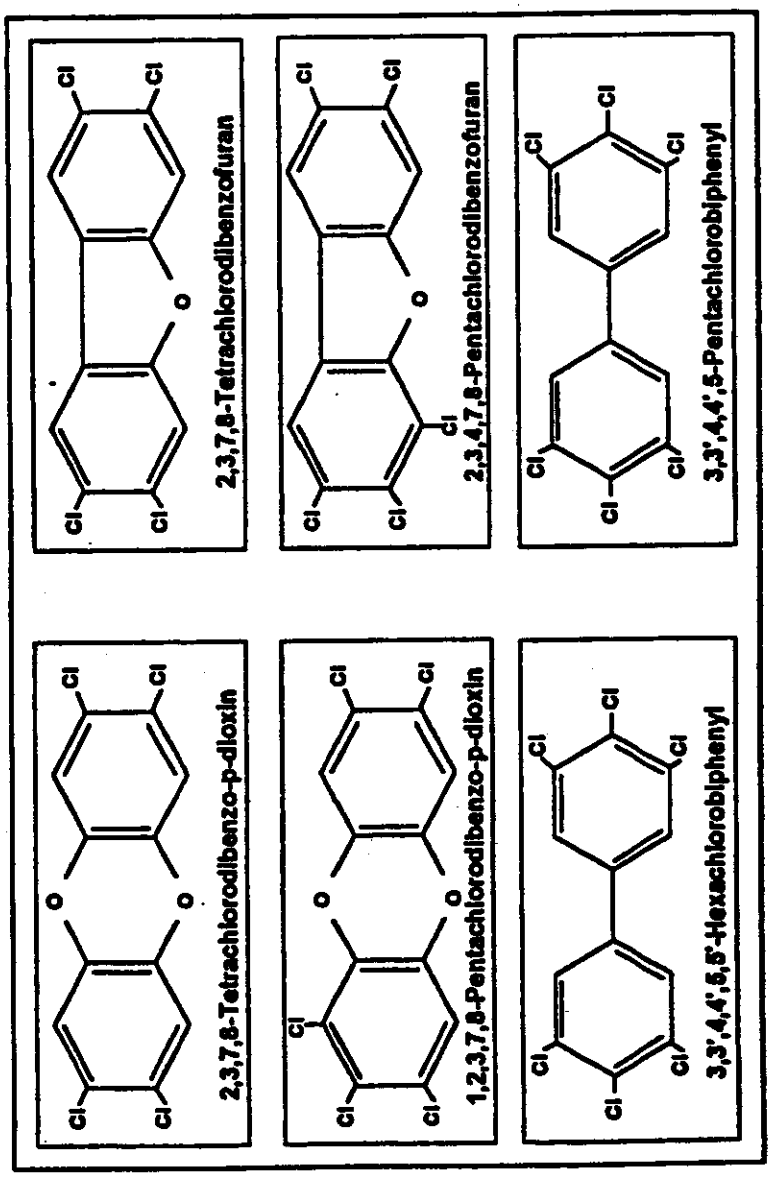

Figure 9-1. Dioxin and similar compounds--chemical structure

Table 9-1. Toxicity Equivalency Factors (TEF) for CDDs and CDFs

Compound	TEF
Mono-, Di-, and Tri-CDDs	0
2,3,7,8-TCDD	1
Other TCDDs	0
2,3,7,8-PeCDD	0.5
Other PeCDDs	0
2,3,7,8-HxCDD	0.1
Other HxCDDs	0
2,3,7,8-HpCDD	0.01
Other HpCDDs	0
OCDD	0.001
Mono-, Di-, and Tri-CDFs	0
2,3,7,8-TCDF	0.1
Other TCDFs	0
1,2,3,7,8-PeCDF	0.05
2,3,4,7,8-PeCDF	0.5
Other PeCDFs	0
2,3,7,8-HxCDF	0.1
Other HxCDFs	0
2,3,7,8-HpCDF	0.01
Other HpCDFs	0
OCDF	0.001

Source: EPA, 1989.

compounds. Dioxin-like PCBs may be responsible for approximately one-fourth to one-half of the total toxicity equivalence associated with general population environmental exposures to this class of related compounds. Both the refinement of the toxicity equivalence factors for dioxin-like PCB congeners (DeVito et al., 1993) as well as a compilation and analysis of all available data on relative toxicities of dioxin-like PCBs with respect to a number of end points (Ahlborg et al., 1994) support these findings. Although these findings have been published recently, additional review and data collection will be needed. In addition, this panel urged investigation of companion TEFs for ecotoxicological use, based on data from ecotoxicological studies.

Throughout this document, concentrations of dioxin and related compounds will be presented as TEQs. TEQs are determined by summing the products of multiplying concentrations of individual dioxin-like compounds times the corresponding TEF for that compound. At times, levels will be presented as concentrations of TCDD because many past studies monitored this congener alone. At most times, TEQs for CDDs and CDFs will be discussed. When TEQ values include the dioxin-like PCBs as well, this will be specifically mentioned. Readers of this chapter are encouraged to review previous chapters in the Health Assessment Document and the Exposure Document for more details on estimates of TEQ presented in this chapter. The strengths and weaknesses as well as the uncertainties associated with the TEF/TEQ approach are discussed later in this chapter.

There are 75 individual compounds comprising the CDDs, depending on the positioning of the chlorine(s), and 135 different CDFs. These are called individual congeners. Likewise, there are 75 different positional congeners of BDDs and 135 different congeners of BDFs (see Exposure Document, Table 2-1). Only 7 of the 75 congeners of CDDs or of BDDs are thought to have dioxin-like toxicity; these are ones with chlorine/bromine substitutions in, at least, the 2, 3, 7, and 8 positions. Only 10 of the 135 possible congeners of CDFs or of BDFs are thought to have dioxin-like toxicity; these also are ones with substitutions in the 2, 3, 7, and 8 positions. While this suggests 34 individual CDDs, CDFs, BDDs, or BDFs with dioxin-like toxicity, inclusion of the mixed chloro/bromo congeners substantially increases the number of possible congeners with dioxin-like activity. There are 209 PCB congeners. Only 13 of the 209 congeners are

thought to have dioxin-like toxicity; these are PCBs with 4 or more chlorines with just 1 or no substitution in the ortho position. These compounds are sometimes referred to as coplanar, meaning that they can assume a flat configuration with rings in the same plane. Similarly configured polybrominated biphenyls are likely to have similar properties; however, the data base on these compounds with regard to dioxin-like activity has been less extensively evaluated. Mixed chlorinated and brominated congeners also exist, increasing the number of compounds considered dioxin-like. The physical/chemical properties of each congener vary according to the degree and position of chlorine and/or bromine substitution. Very little is known about occurrence and toxicity of the mixed (chlorinated and brominated) dioxin, furan, and biphenyl congeners.

In general, these compounds have very low water solubility, high octanol-water partition coefficients, and low vapor pressure and tend to bioaccumulate. Volume II of the Exposure Document presents congener-specific values for water solubility, vapor pressure, partition coefficients, and photo quantum yields and discusses other physicochemical characteristics of the chlorinated dioxins and dibenzofurans. These physicochemical properties result in the environmental fate and transport discussed below. Expanded discussions will be required in future documents to account for dioxin-like PCBs and for brominated or mixed halogenated congeners.

9.3. ENVIRONMENTAL FATE

Despite a growing body of literature from laboratory, field, and monitoring studies examining the environmental fate and environmental distribution of CDDs and CDFs, the fate of these environmentally ubiquitous compounds is not yet fully understood, and the following represents our best understanding, based on available data. In soil, sediment, the water column, and probably air, CDDs/CDFs are primarily associated with particulate and organic matter because of their high lipophilicity and low water solubility. They exhibit little potential for significant leaching or volatilization once sorbed to particulate matter. The available evidence indicates that CDDs and CDFs, particularly the tetra- and higher chlorinated congeners, are extremely stable compounds under most environmental conditions, with environmental persistence measured in decades. The only environmentally significant

transformation process for these congeners is believed to be photodegradation of chemicals not bound to particles in the gaseous phase or at the soil- or water-air interface. Brominated congeners are significantly more readily transformed by photodegradation. CDDs/CDFs entering the atmosphere are removed either by photodegradation or by dry or wet deposition. Although some volatilization of dioxin-like compounds on soil does occur, the predominant fate of CDDs/CDFs sorbed to soil is to remain in place near the surface of undisturbed soil or to move to water bodies with erosion of soil. CDDs/CDFs entering the water column primarily undergo sedimentation and burial. The ultimate environmental sink of these CDDs/CDFs is believed to be aquatic sediments.

Little specific information exists on the environmental transport and fate of the dioxin-like PCBs. However, the available information on the physical/chemical properties of dioxin-like PCBs, coupled with the body of information available on the widespread occurrence and persistence of PCBs in the environment, indicates that these PCBs are likely to be associated primarily with soils and sediments and to be thermally and chemically stable. Soil erosion and sediment transport in water bodies and emissions to the air (via volatilization, dust resuspension, or point source emissions) followed by atmospheric transport and deposition are believed to be the dominant transport mechanisms responsible for the widespread environmental occurrence of PCBs. Photodegradation to less chlorinated congeners followed by slow anaerobic and/or aerobic biodegradation is believed to be the principal path for destruction of PCBs. Similar situations exist for the polybrominated biphenyls (PBBs). Little information is available on the occurrence and fate of biphenyl congeners containing both chlorine and bromine, but their contribution to dioxin-like activity in the environment is thought to be small.

9.4. SOURCES

The chlorinated and brominated dioxins and furans have never been intentionally produced other than on a laboratory-scale basis for use in chemical analyses. Rather, they are generated as by-products from various combustion and chemical processes. PCBs were produced in relatively large quantities for use in such commercial products as dielectrics, hydraulic fluids, plastics, and paints. They are no longer produced in the United States but

continue to be released to the environment through the use and disposal of these products. A similar situation exists for the commercially produced PBBs, which were produced for a number of uses like flame retardants.

Dioxin-like compounds are released to the environment in a variety of ways and in varying quantities, depending on the source. Studies of sediment cores in lakes near industrial centers of the United States have shown that historical environmental deposition of dioxins and furans was quite low until about 1920, peaked around 1980, and has declined thereafter. This trend suggests that the presence of dioxin-like compounds in the environment has occurred primarily as a result of industrial practices and is likely to reflect changes in release over time. Further work to confirm declining trends in environmental samples and to relate these data to human exposures will be required.

Although these compounds are released from a variety of sources, the congener profiles of CDDs and CDFs found in sediments have been linked to combustion sources (Hites, 1991). Three theories have been suggested to explain formation of CDDs and CDFs during combustion: (1) CDDs and CDFs are present in the fuels or feed materials and pass through the combustor intact; (2) precursor chemicals are present in the fuels or feed material and undergo reactions catalyzed by particulates and other chemicals to form CDDs and CDFs; and (3) the CDDs and CDFs are formed de novo from organic and inorganic substrates bearing little resemblance in molecular structure.

The principal identified sources of environmental release of CDDs and CDFs may be grouped into four major types:

- Combustion and Incineration Sources: Dioxin-like compounds can be generated and released to the environment from various combustion processes when chlorine donor compounds are present. These sources can include incineration of wastes such as municipal solid waste, sewage sludge, hospital and hazardous wastes; metallurgical processes such as high-temperature steel production, smelting operations, and scrap metal recovery furnaces; and the burning of coal, wood, petroleum products, and used tires for power/energy generation.

- Chemical Manufacturing/Processing Sources: Dioxin-like compounds can be formed as by-products from the manufacture of chlorine and such chlorinated compounds as chlorinated phenols (e.g., pentachlorophenol), PCBs, phenoxy herbicides (e.g., 2,4,5-T), chlorinated benzenes, chlorinated aliphatic compounds, chlorinated catalysts, and halogenated diphenyl ethers. Although the manufacture of many chlorinated phenolic intermediates and products, as well as PCBs, was terminated in the late 1970s in the United States, production continued elsewhere around the world until 1990, and continued, limited use and disposal of these compounds can result in releases of CDDs, CDFs, and PCBs to the environment.
- Industrial/Municipal Processes: Dioxin-like compounds can be formed through the chlorination of naturally occurring phenolic compounds such as those present in wood pulp. The formation of CDDs and CDFs resulting from the use of chlorine bleaching processes in the manufacture of bleached pulp and paper has resulted in the presence of CDDs and CDFs in paper products as well as in liquid and solid wastes from this industry. Municipal sewage sludge has been found to occasionally contain CDDs and CDFs.
- Reservoir Sources: The persistent and hydrophobic nature of these compounds causes them to accumulate in soils, sediments, and organic matter and to persist in waste disposal sites. The dioxin-like compounds in these "reservoirs" can be redistributed by various processes such as dust or sediment resuspension and transport. Such releases are not original sources in a global sense, but can be on a local scale. For example, releases may occur naturally from sediments via volatilization or via operations that disturb them, such as dredging. Aerial deposition and accumulation on leaves can lead to releases during forest fires or leaf composting operations.

As awareness of these possible sources has grown in recent years, a number of changes have occurred in the United States, which should reduce the release rates. For example, releases of dioxin-like compounds have been reduced due to the switch to unleaded automobile fuels (and associated use of catalytic converters and reduction in halogenated

scavenger fuel additives), process changes at pulp and paper mills, new emission standards and upgraded emission controls for incinerators, and reductions in the manufacture of chlorinated phenolic intermediates and products and the use of pesticides such as 2,4,5,-T and pentachlorophenol.

Although dioxins in the environment may arise from a number of sources as discussed above, the Exposure Document presents recent analyses of only air emissions of CDDs and CDFs for several European countries in terms of total toxic equivalents based on international TEFs for CDDs and CDFs. These studies assume that emissions to air make up the major portion of dioxins released to the environment. Estimates of total release in these countries range from approximately 100-1,000 g TEQ/year in West Germany and 100-200 g TEQ/year in Sweden to approximately 1,000 and 4,000 g TEQ/year maximum emissions in The Netherlands and United Kingdom, respectively. Similar nationwide estimates for the United States have not been compiled prior to this reassessment effort. The Exposure Document estimates the U.S. emissions to be in the range of 3,300-26,000 g TEQ/year, with a central estimate of 9,300 g TEQ/year. These estimates were derived from data from emission tests at relatively few facilities in each combustor class. These data were used to develop emission factors and then extrapolated to a nationwide basis using the total amount of waste feed material in each class. Variability of measured emissions from facilities within a class and the uncertainty in estimating the total amount of waste feed material in each class lead to the wide range presented above. Qualitatively speaking, major contributors to this total include medical waste incinerators, municipal waste incinerators, cement kilns, and industrial wood burning. Because of the limited number of measurements and the large number of potential sources for each of these emissions, total estimated emissions from these sources are considered highly uncertain. Municipal waste incineration has more measurement data than other air sources, but emissions are highly variable among facilities so that the overall estimate remains uncertain. Diesel-fueled vehicles, hazardous waste burning, forest fires, and metal smelting are more moderate contributors of dioxin-like compounds, but the magnitude of the contribution is also highly uncertain. Sewage waste incineration and residential wood burning as well as a few minor processes round out the current analysis and provide lower range estimates of medium to low certainty. Although

still other sources are recognized and releases to land and water in addition to air are discussed in the Exposure Document, it is clear from this exercise that additional measurement data will be needed to gain an adequate appreciation for the nature and magnitude of major U.S. sources of CDD and CDF emissions.

Several investigators have attempted to conduct "mass balance" checks on the estimates of national dioxin releases to the environment. Basically, this procedure involves comparing estimates of the emissions to estimates of aerial deposition. Such studies in Sweden (Rappe, 1991) and Great Britain (Harrad and Jones, 1992) have suggested that the deposition exceeds the emissions by about tenfold. These studies are acknowledged to be quite speculative due to the strong potential for inaccuracies in emission and deposition estimates. In addition, the apparent discrepancies could be explained by long-range transport from outside the country, resuspension, and deposition of reservoir sources or unidentified sources. Bearing these limitations in mind, this procedure has been used in this reassessment to compare the estimated emissions and deposition in the United States.

Deposition measurements have been made at a number of locations in Europe and two places in the United States (see discussion of these studies in Volume II of the Exposure Document). These limited data suggest that a deposition rate of 1 ng TEQ/m^2-yr is typical of remote areas and that 2-6 ng TEQ/m^2-yr is more typical of populated areas. Applying these values, the total U.S. deposition can be estimated as 20,000 to 50,000 g TEQ/yr. This range can be compared to the range of emissions for the United States (3,300-26,000 g TEQ/yr) as presented in the Exposure Document. As noted above, interpreting such comparisons is highly speculative and supports the need to conduct further emissions testing into all media and deposition measurement, if we are to understand the total mass balance for these compounds.

While all of the above emission and deposition values are given in the form of TEQs, it should be noted that neither emission nor deposition is equivalent to exposure or intake. Significant changes in composition can occur to complex mixtures of CDDs, CDFs, and PCBs as they move through the environment. Measurements at or near the point of human contact provide the best estimates of human exposure. TEQs are most relevant to potential for hazard and risk when they represent intake values.