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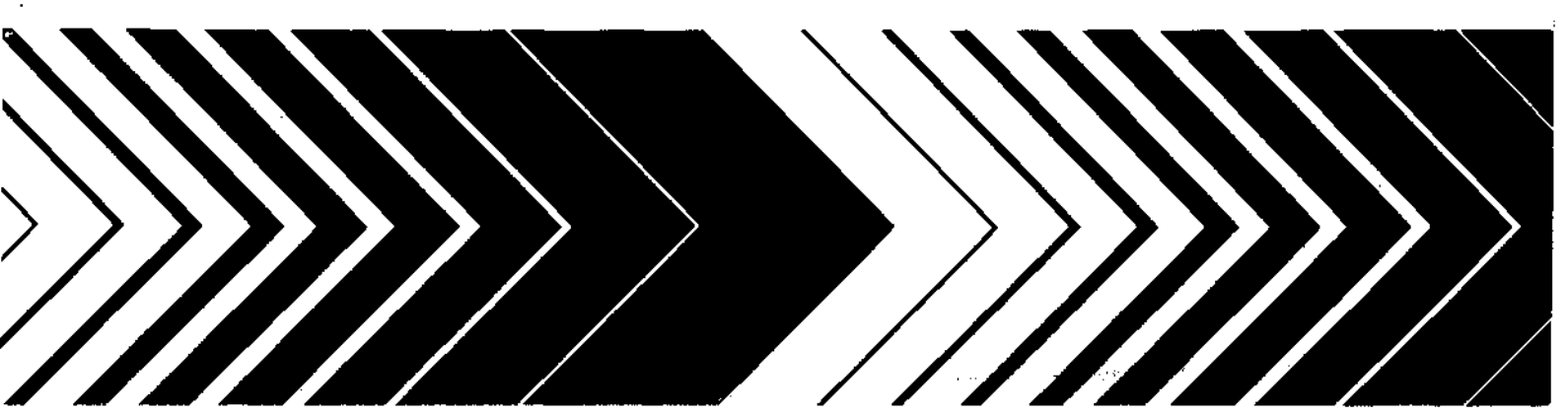
# Report of the Research Planning Workshop on Bioavailability of Dioxins



EPA/600/9-86/004
January 1986

# REPORT OF THE RESEARCH PLANNING WORKSHOP ON BIOAVAILABILITY OF DIOXINS

RALEIGH, N.C.
SEPTEMBER 1984

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF RESEARCH AND DEVELOPMENT
WASHINGTON, DC 20460

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## FOREWORD

Research on the class of compounds called dioxins began several decades ago, but the research activity increased substantially in the 1960s and 1970s, when the complex problem of dioxin contamination received national and international attention. Although considerable research has been done in this field, there are certain gaps in scientific knowledge, related to understanding the bioavailability of dioxins, that need to be identified to evaluate more accurately human and environmental risks associated with these chemicals.

To accomplish this goal, the EPA Office of Research and Development sponsored the Research Planning Workshop on the Bioavailability of Dioxins, September 9-12, 1984, that brought together scientists and managers in various aspects of dioxin work from government agencies, academia, and industry. About ninety researchers focused their attention during the four-day meeting on identifying the most obvious gaps in knowledge and the consequent research needs.

This report is the outcome of the workshop; it addresses the current state of knowledge on dioxins and defines the research needs perceived by top scientific experts in this field. Because of the range and complexity of this scientific area, the report is divided into three main parts to address different aspects of bioavailability: environmental processes that determine bioavailability, the bioavailability to ecosystems, and the bioavailability to humans. This document is primarily intended for use by the Agency to plan future research programs. We also hope this document will be useful to other research organizations in both the government and private sectors.

Erich Bretthauer
Director
Office of Environmental
Processes and Effects
Research

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## ACKNOWLEDGMENTS

The contributions of all workshop participants are gratefully acknowledged, especially Rizwanul Haque of EPA who served as chairperson of the workshop. The success of the workshop and this report were possible because of the assistance of the co-chairpersons: Diane Courtney, Thomas Duke, and Walter Sanders, U.S. Environmental Protection Agency; Michael Gallo, UMDNJ-Rutgers Medical School; Mark Harwell, Cornell University; and Captain Terry Stoddart, U.S. Air Force.

The efforts of Dan Tisch, Workshop Coordinator, and Linda Cooper, Technical Editor, Northrop Services, Incorporated, in coordinating the workshop and in producing this report are also acknowledged. The final version of this report was integrated and edited by Christine C. Harwell. We also thank Janice Wilson, Word Processing Specialist, Northrop Services, Incorporated, and Roberta Sardo and Carin Rundle of Cornell University for their efforts in producing this report.

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## EXECUTIVE SUMMARY

The goal of the Research Planning Workshop on Bioavailability of Dioxins was to evaluate the ongoing research on the bioavailability of chlorinated dioxins and related chemicals, to identify research needs, and to develop a focused research plan. Workshop participants were organized into three groups that addressed the topics: environmental processes in bioavailability, bioavailability to ecosystems, and bioavailability to humans.

Each group of participants at the workshop addressed specific areas regarding bioavailability, within the broad range of dioxin research, and identified areas for study in their final summary reports. However, the definition and concept of bioavailability varied among the three groups. One group addressed dioxins in general, while the other two groups focused discussions on 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). Because the class of dioxins represents a large number of chemicals and most attention to date has been focused on the isomer 2,3,7,8-TCDD, special terminology is used in this document to address these chemicals: the term TCDD refers to 2,3,7,8-TCDD; the term dioxins refers to other isomers.

### Environmental Processes In Bioavailability

The group dealing with the environmental processes in the bioavailability of TCDD evaluated the current state of the art in analytical methods, physical and chemical properties, transport and transformation processes, and exposure modelling. The group addressed the basic scientific understanding required for valid estimation of exposure, bioavailability, and risk. The group identified major gaps in knowledge and prioritized the research needs in these areas. In ranking the research objectives, the group considered both short- and long-term needs.

#### Photochemical Processes

Available information indicates that photolysis offers the most promising environmental process for degrading TCDD. Therefore, the highest research priority was assigned to better characterization of the rates and extent of direct and indirect photolysis in air, on surfaces, and in water.

#### Physical and Chemical Properties

The second research priority concerns the expansion of the data base covering physical and chemical properties of TCDD and related compounds. The use of structure-activity relationships, based on thermodynamic laws, to predict physical and chemical properties offers a cost-effective alternative to numerous laboratory determinations.

**Sorption/Desorption/Volatilization**

To understand better the dynamics of TCDD movement in all environmental media, extensive studies of sorption/desorption phenomena are needed. Specifically, the effects of organic content of soils and sediments on the sorption/desorption of TCDD from the saturated and unsaturated zones require further study, as do the effects of particulates on TCDD in the atmosphere.

**Chemical Transformations**

The chemical transformations of TCDD have not been characterized. A complete definition of the transformation processes will contribute greatly to the understanding of transport as well as provide indications of specific chemical reactions that may be employed to degrade TCDD. The ability of TCDD to undergo oxidation/reduction, acid/base hydrolysis, nucleophilic displacement, and metal chelation reactions needs to be determined.

**Biological Processes**

The use of biodegradation as a cost-effective procedure for TCDD degradation must be ranked as a long-term, high-priority research need. Because the genes for TCDD metabolism have been demonstrated in higher organisms, the employment of recombinant DNA technology to construct a microorganism capable of TCDD degradation may greatly benefit future cleanup operations and reduce the risk to the environment and human populations.

**Intermedia Transport**

Although the rates of certain intermedia transfers can be predicted, appropriate measurement techniques are not available to validate the predictions. The bulk transport and intermedia transfer of TCDD require further characterization. The movement of TCDD-contaminated particles appears to be a critical link in the bioavailability of TCDD.

**Modelling**

Currently available mathematical exposure models are applicable to predict the exposure concentrations of TCDD in the various environmental media, if and when the various equilibrium and rate coefficients have been determined. However, research will be required to apply and test the various media and multimedia models to determine their degree of applicability, precision, and accuracy.

**Surrogate Parameters for Combustion**

The production of dioxins and furans from municipal incinerators is well documented. Identification and measurement of these chemical species are costly. To control effectively the combustion process so that the release of these compounds is eliminated, new surrogate parameters for process control are needed.

## Need for Sufficient Supplies of TCDD for Research

An adequate supply of TCDD and laboratory standards for all possible isomers of dioxins and furans is not readily available. These materials are required for quality assurance and quality control and to facilitate investigations of dioxin and furan distribution in the environment. An appropriate toxicological evaluation of dioxins and furans cannot be conducted without the appropriate laboratory standards.

## Bioavailability In Ecosystems

To gain a better understanding of the pathways to humans and effects on the ecosystem, the fate and transport of dioxin in the environment must be determined. This determination includes addressing areas such as the bioavailability of dioxin to biota, and how organisms influence the transport of dioxins within and across systems. Also of interest are rates of exchange, such as the rate of dioxin uptake by plants from soil, and the ultimate partitioning of the chemical.

To clarify such interactions, results of group discussion are presented in a section on a conceptual framework for exchanges of dioxin among ecosystem components, followed by sections on aquatic and terrestrial ecosystems with respect to fate, transport, effects on biota (species and processes), and pathways to humans.

In these sections, three sets of topics were considered: 1) identification of ecosystem processes that a.) are involved in routes, rates, and reservoirs of dioxins in aquatic and terrestrial ecosystems; b.) are particularly susceptible to effects of dioxin contamination; or c.) are involved in biological decontamination processes; 2) identification of particular species and communities that are impacted or potentially impacted by dioxins; and 3) identification of the role of food chains and webs in human exposure and risk.

## Research Needs

Data on the impact of dioxins at the ecosystem level are essentially nonexistent, and relatively few data are available describing the effects of these chemicals on single species. Therefore, many research needs were identified by group participants; the following were considered the highest priority:

- Develop the capability to predict dioxin levels in tissues (particularly in organisms that constitute human food chains) as a function of environmental conditions; develop toxicity data for understanding the mechanisms of toxicity and the factors responsible for differences in sensitivities among species.

- Measure the concentration of dioxins over time in organisms as a function of dose in food, water, and other sources for model development. Use microcosms for model verification.

- Conduct a full-scale ecological study at a highly contaminated site. Include field studies of fate, chronic effects, and ecological processes, with supporting laboratory studies.

- Evaluate the chemical and biological characteristics of residue from experimental incineration projects and incorporate results in risk assessment.

In addition to these research needs, there is a need to improve risk assessment capability and to evaluate the uncertainties resulting from conflicting data, unexpected indirect effects, and laboratory-to-field extrapolations.

## Bioavailability To Humans

Risks may be inaccurately estimated in the absence of knowledge about factors determining bioavailability, even when exposure is relatively well defined. Clearly, matrix and route effects are likely to be significant. However, human responses and risk are also influenced by exposure and by differences in the sensitivity of target sites of action. To consider bioavailability adequately, exposure and toxic response must also be examined.

The following research needs were identified to evaluate the bioavailability of TCDD relative to human health.

### Matrices

The bioavailability of TCDD from matrices of soil, fly ash, and respirable particles should be determined using the same species and same toxicologic end points. A range of concentrations should be utilized, because the bioavailability of TCDD may differ at differing concentrations levels.

### Host Factors; Deposition and Mobilization of TCDD

Because of the lack of knowledge of the critical target organ(s) in humans, studies are needed to determine the appropriate animal species to use as models for studying host factors, tissue distribution, and mobilization from body stores. Additionally, the critical end points and other biochemical markers need to be determined for both human and other animal models.

One of the sensitive end points in animals and possibly humans is the immune system. The data that are available indicate further studies are needed of the effects of TCDD on the immune system.

The body burden of TCDD in humans needs to be determined using adipose tissue as the most important depot. Studies determining the residue of TCDD in other organs might indicate possible target organs, as well as the mobilization, redistribution, metabolic pathways, and secretion or excretion patterns in humans.

### Pharmacokinetics and Structure-Activity Relationships

Because humans are often exposed to mixtures of compounds that would include TCDD and similar chemicals, studies are needed to delineate the interactive effects of dioxin and furan isomers with TCDD, and to determine the additive, synergistic, or antagonistic effects, as well as the pharmacodynamics of the mixtures and receptor level modulations.

### Extrapolation of Animal Data to Humans

An animal model that best indicates TCDD toxicity in humans is still being developed according to the criteria more fully discussed in Chapter 3. Because there are so many manifestations of TCDD toxicity, it may be necessary to have more than one model, depending on the end point.

### Epidemiological Studies

Methods need to be developed to identify persons who have been exposed to TCDD and related compounds as a basis for epidemiological studies. Additional studies in humans should be done with cohorts not exposed to TCDD to establish the baseline for the end points of toxicity. Rigorous epidemiological studies with sound methods and proper execution are needed to determine the effects of TCDD in humans. Until there are better epidemiological studies, the determination of TCDD toxicity will not be known with any assurance, and the extrapolation of animal data to humans cannot be done reliably.

### Assay of TCDD

To perform many of the suggested studies, there is a need to develop and validate assays of TCDD that are rapid and economical, either in vivo or in vitro, and that can be used to determine the concentration of TCDD in various organs.

## INTRODUCTION

The class of chemicals polychlorinated dibenzo dioxins, commonly known as dioxins, has attracted great attention and raised controversies during recent years. In the United States, issues about dioxins surfaced during the 1960s, when 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) was found to be a contaminant in the commonly used herbicide 2,4,5-T (2,4,5-trichlorophenoxy-acetic acid). The high toxicity and persistence of 2,3,7,8-TCDD in the environment represent the primary characteristics of dioxins that pose risks to human health and the environment. Because the class dioxins represents a large number of chemicals and most attention to date has been focused on the isomer 2,3,7,8-TCDD, special terminology is used in this document to address these chemicals: the term TCDD refers to 2,3,7,8-TCDD; the term dioxins refers to other isomers.

Since the 1960s, several incidents have focused attention on the contamination problem: the human and environmental exposure to dioxins as a result of a chemical plant accident in Seveso, Italy; the identification of dioxins at several hazardous waste sites in the states of Missouri, New Jersey, New York, and Arkansas; and the occurrence of dioxins in fish samples in the states of Michigan and Wisconsin. Dioxins are also associated with combustion processes and are found in municipal incinerator fly ash.

In spite of the release of dioxins to the environment and concomitant potential exposure of humans, the pathways and persistence have not been fully investigated for many environments. Additional study is required on dioxin accumulation and partitioning in living systems, the toxicity associated with dioxins, the evaluation of the human and environmental risks, and the development of control technologies necessary to minimize such risks. This information is crucial to making appropriate regulatory decisions about dioxins under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Toxic Substances Control Act (TSCA), the Resource Conservation and Recovery Act (RCRA), and the Comprehensive Environmental Response Compensation and Liability Act (CERCLA or Superfund).

Central to the complex issues of exposure and risk assessment is the evaluation of the bioavailability of dioxins. The term bioavailability has not been clearly defined, and the subject remains poorly understood. It involves the understanding of factors related in the uptake, release, or bioaccumulation of dioxins by living organisms. Recent findings at the National Institute of Environmental Health Sciences indicate that TCDD was bioavailable to laboratory animals fed with contaminated soils from Missouri. But a similar experiment done with New Jersey soil indicated that dioxin was not detected in the bodies of laboratory animals. To understand the complex issues of bioavailability, the environmental processes that can influence bioavailability to ecosystems and humans must be characterized. Identification and quantification of TCDD and other dioxins in environmental and biological matrices also require major

attention. Most research data deal with TCDD; the toxic effects and environmental risks associated with other dioxins also need to be evaluated.

Dioxin research currently funded by the U.S. Environmental Protection Agency (EPA) addresses four main areas: 1) development of measurement methods and quality assurance procedures for identifying and quantifying dioxins; 2) development and evaluation of control technologies for containment and destruction of dioxins; 3) study of the fate of dioxins in soils and investigation of the uptake of dioxins by plants and animals; and 4) assessment of health and environmental risk associated with dioxins.

Because understanding the bioavailability of dioxins is essential to understanding toxicity and risk, a workshop was held to obtain input in developing a focused research plan. Scientists attending represented a broad range of expertise from research groups in academia, industry, and government organizations. The goal of this workshop was to evaluate the ongoing research on the bioavailability of chlorinated dioxins and related chemicals, identify research needs, and develop a focused research plan. Workshop participants were organized into three groups that addressed the topics: 1) environmental processes in bioavailability; 2) bioavailability to ecosystems; and 3) bioavailability to humans.

The Environmental Processes in Bioavailability Group focused on defining various environmental processes controlling the bioavailability of TCDD in the biosphere. Transformation processes and bioavailability assessments were also discussed in this group. The Bioavailability to Ecosystems Group evaluated the factors relevant to the bioavailability of dioxins in aquatic and terrestrial ecosystems, and the potential impact of these chemicals on ecosystems. Ecosystem processes were identified, particular species and communities that are potentially impacted by dioxins were addressed, and the role of food chains and the food web in human exposure and risks were discussed. The Bioavailability to Humans Group evaluated factors such as the bioavailability of TCDD from environmental matrices, the host factors affecting bioavailability, in vivo bioavailability, routes of exposure, toxic human effects, interspecies differences, and extrapolation from other animals to humans.

This report will be used by EPA in its research planning. We hope that this report will be beneficial to other research organizations in planning their research.

# CHAPTER 1

# ENVIRONMENTAL PROCESSES IN BIOAVAILABILITY

Co-chairpersons: Walter M. Sanders III and Capt. Terry Stoddart

## 1.1 Introduction

The presence of TCDD in the environment poses great concern because of its known toxicity and persistence. Bioavailability of TCDD and other chlorinated aromatic compounds in the environment depends on many factors that control their concentration in the biosphere. Important factors include physical and chemical properties, transport and transformation processes, and characteristics of the environmental media.

One workshop group of scientists and engineers addressed the many complex physical and chemical issues related to the bioavailability of TCDD. The group: 1) evaluated available analytical methods, possible transport pathways, and environmental transformation processes; 2) reviewed the current state of the understanding of bioavailability of dioxins; 3) identified significant research needs; and 4) prioritized the efforts required to bring the state of the art up to an acceptable scientific level to understand human and environmental exposure and risk assessment.

Also considered were the needs for significant supplies of TCDD for research and standards/reference samples for quality assurance and quality control, the applicability of available exposure modelling techniques specifically for TCDD, and the need for surrogate parameters for combustion processes control. The consensus of the group was that the fate of dioxin isomers and related chemicals, such as the polychlorinated dibenzofurans and xanthenes, should be considered along with TCDD as human and environmental toxicology dictates.

The seven highest priority research needs identified by the group are discussed in order of importance, with a statement concerning the current state of the art and research objectives. Three related items, analytical methods, modelling, and surrogate parameters for combustion, were given equal priority, and are also identified below.

| Ranking | Need |
|---|---|
| 1 | Photochemical Processes |
| 2 | Physical and Chemical Properties |
| 3 | Sorption/Desorption/Volatilization |
| 4 | Chemical Transformations |

| Ranking | Need |
|---|---|
| 5 | Biological Processes (Longer-term) |
| 6 | Intermedia Transport |
| 7 | Advection/Diffusion/Dispersion Activities |
| o | Analytical Methodology for Analysis of TCDD in Environmental and Human Samples Modeling |
| o | Modelling |
| o | Surrogate Parameters for Combustion |

These prioritized research needs have been grouped for discussion into five categories: Physical and Chemical Properties, Transformation Processes, Transport Processes, Modelling, and Analytical Methodology for Analysis.

In some cases, the research suggested by this working group related only to TCDD, such as the measurement or validation of the physical and chemical properties of TCDD. In other cases, the recommended research extends the current scientific state of the art for characterizing environmental transport and transformation processes and will be applicable to other hydrophobic organic chemicals. This would include research efforts to characterize, identify, and measure the soil characteristics (e.g., organic and moisture content, particle distribution, and temperature) that govern the rates and extent of the various transport and degradation processes important to TCDD and all other hydrophobic organic chemicals.

Results from the research outlined in this section will have major impacts on the understanding and estimation of the bioavailability of TCDD to both humans and ecosystem components. For example, if volatilization from sorbed surfaces at night is a significant transport pathway, inhalation or dermal contact with vapor-phase TCDD will be an exposure route that must be considered. Results from this research will also apply directly to the modification of regulatory criteria and standards by providing more accurate identifications of exposure pathways and rates. Likewise, results may impact the treatment and control of TCDD-contaminated areas if direct vapor-phase photolysis or biodegradation mediated by genetically engineered microorganisms could be incorporated into significant in-place treatment processes.

### 1.2 Physical And Chemical Properties

The known physical and chemical properties for TCDD are summarized in Table 1.1, which includes literature values for measured and estimated properties and values measured by Schroy and associates. Values not available from laboratory work or literature were estimated. Comparable data for other dioxins, furans, and other very low volatility chemicals are not available.

**Research Needs**

Reasonable estimates of physical and chemical properties of TCDD isomers, other dioxins, and furans in general are necessary to permit rational analysis of their behaviorwithin the biosphere. The structure-activity relationship approach, based on thermodynamic consideration, represents a cost-effective alternative for this purpose

Table 1.1

PHYSICAL PROPERTY DATA SHEET[a]

| | | | | | |
|---|---|---|---|---|---|
| CHEMICAL NAME | 2,3,7,8-Tetrachlorodibenzo-p-dioxin (Synonym 2,3,7,8-TCDD or Dioxin) CAS # - 1746 -01 - 6 | | SPECIFIC HEAT,J/(°K-gmol) gas @25°C | 250.92* | (SHA) |
| CHEMICAL FORMULA | $C_{12}H_4O_2Cl_4$ | | HEAT OF VAPORIZATION | | |
| | | | @NBP, kJ/gmol | 71.81* | (RPS) |
| | | | @NBP, BTU/lb | 95.95* | (RPS) |
| MOLECULAR WEIGHT | 321.974 | (IUPAC) | @MP, kJ/gmol | 85.00* | (MON) |
| | | | @MP, cal/g | 63.10* | (MON) |
| | | | @MP, BTU/lb | 113.57* | (MON) |
| CRITICAL CONSTANTS | | | | | |
| P = Pressure, Pa | 2372.829* | (RPS) | HEAT OF FUSION | | |
| T = Temperature, K | 934.5 * | (RPS) | @MP, kJ/gmol | 38.91 | (BRM) |
| Z = Compressibility | 0.233* | (RPS) | @MP, cal/g | 28.88 | (BRM) |
| V = Volume, $cm^3$ | 763 * | (RPS) | @MP, BTU/lb | 51.99 | (BRM) |
| DENSITY, g/ml | | | HEAT OF SUBLIMATION | | |
| Solid @ 25°C | 1.827* | (BRM) | @MP, k/gmol | 123.91 | (MON) |
| Solid/Liquid @ MP | 1.720* | (RPS) | @MP, cal/g | 91.98 | (MON) |
| Liquid @ NBP | 1.021* | (RPS) | @MP, BTU/lb | 165.56 | (MON) |
| VAPOR PRESSURE | | | HEAT OF FORMATION | | |
| Pascals @ 30.1°C | 4.68 E-7 | (MON) | gas @25°C, k/gmol | -205.43* | (SFT) |
| Pascals @ 54.6°C | 1.84 E-5 | (MON) | | | |
| Pascals @ 62.°C | 5.03 E-5 | (MON) | FREE ENERGY OF FORMATION | | |
| Pascals @ 71.°C | 1.61 E-4 | (MON) | gas @25°C, kJ/gmol | -195.18* | (SHA) |

Table 1.1 (cont.)

PHYSICAL PROPERTY DATA SHEET

ANTOINE CONSTANTS T = 10 to 420°C

| Units log e, Pa & K | | | |
|---|---|---|---|
| Temp. Range | 10 to 305°C | 305 to 420°C | |
| A | 34.57083 | 25.10435* | |
| B | 14903.438 | 9430.391* | |
| C | 0.00 | 0.00* | |
| | (MON) | (MON) | |

NORMAL BOILING POINT (NBP) @ 1 atm

| | | |
|---|---|---|
| Degrees C | 421.4 * | (MON) |
| Degrees K | 684.52* | (MON) |
| Degrees F | 790.5 * | (MON) |
| Degrees R | 1250.14* | (MON) |

FREEZING POINT

| | | |
|---|---|---|
| °C | 305.0 | (BRM) |

SOLUBILITY IN (@ 1 atm)

| | T = °C | milligrams/liter | |
|---|---|---|---|
| Water | 22 | 0.00000791 | (ADB) |
| Agent Orange | 25 | 580 | (VA) |
| o-Dichloro-benzene | 25 | 1400 | (ETD) |
| Chlorobenzene | 25 | 720 | (ETD) |
| Benzene | 25 | 570 | (ETD) |
| Chloroform | 25 | 370 | (ETD) |
| n-Octanol | 25 | 48 | (ETD) |

HEAT OF COMBUSTION

| | | |
|---|---|---|
| gas @25°C, kJ/gmol | -5000.3* | (SFT) |

ENTROPHY @ 101.325 kPa

| | | |
|---|---|---|
| gas @25°C, kJ(°K-gmol) | 478.06* | (SHA) |

SCHMIDT NUMBER (vapor in air @ dilute conc.)

| | | |
|---|---|---|
| Dimensionless @25°C | 3.370* | (RPS) |

DIFFUSIVITY (IN WATER)

| | | |
|---|---|---|
| $D/cm^2/sec$ | 5.6 E-6 | (RPS) |

PARTITION COEFFICIENTS, g/g

| | | |
|---|---|---|
| Octanol/Water | 1,400,000* | (KEN) |
| Octanol/Water | 1,400,000* | (MON) |
| Organic Solids/Water | 468,000* | (KEN) |
| Biota/Water | 35,500* | (KEN) |
| Cattle Feed/Fat | 3.5 | (KEN) |

PARTITION COEFFICIENT, mole fraction/mole fraction

| MATERIAL | T = °C | "M" for AIR/MATERIAL | | |
|---|---|---|---|---|
| Water | 22 | 2.709 | | (CALC) |
| Agent Orange | 25 | 4.9 | E-9 | (CALC) |
| o-Dichloro-benzene | 25 | 4.2 | E-9 | (CALC) |
| Chlorobenzene | 25 | 9.09 | E-9 | (CALC) |

Table 1.1 (cont.)

PHYSICAL PROPERTY DATA SHEET

| | | | | |
|---|---|---|---|---|
| Methanol | 25 | 10 | | (ETD) |
| Acetone | 25 | 110 | | (ETD) |
| ACTIVITY COEFFICIENTS AT INFINITE DILUTION IN | | | | |
| | T = °C | GAMMA | | |
| Water | 22 | 2.26 | E12 | (CALC) |
| Agent Orange | 25 | 2368 | | (CALC) |
| o-Dichloro-benzene | 25 | 2043 | | (CALC) |
| Chlorobenzene | 25 | 4394 | | (CALC) |
| Benzene | 25 | 6356 | | (CALC) |
| Chloroform | 25 | 10854 | | (CALC) |
| n-Octanol | 25 | 4270 | | (CALC) |
| Methanol | 25 | 796000 | | (CALC) |
| Acetone | 25 | 39864 | | (CALC) |
| HENRY'S LAW CONSTANT FOR AIR/WATER SYSTEM | | | | |
| H, atm $m^3$/gmol | | 4.88 | E-5* | (CALC) |
| Benzene | 25 | 1.3 | E-8 | (CALC) |
| Chloroform | 25 | 2.25 | E-8 | (CALC) |
| n-Octanol | 25 | 8.8 | E-8 | (CALC) |
| Methanol | 25 | 1.6 | E-6 | (CALC) |
| Acetone | 25 | 8.25 | E-8 | (CALC) |

| | | |
|---|---|---|
| ENVIRONMENTAL FACTORS | | |
| Oxygen Demand | | |
| ThOD, lb $O_2$/lb chemical | 1.193 | (CALC) |
| IMMEDIATELY DANGEROUS TO LIFE AND/OR HEALTH | | |
| ppm | 0.001* | (CDC) |
| SAFETY | | |
| Acute Toxicity | | |
| oral (guinea pigs) LD LO, mg/kg | 0.0006 | (CAD) |

[a] Prepared by J.M. Schroy (1984). Physical properties without asterisks (*) are reported as measured values, but those with asterisks have been reported as estimated by the author referenced or by a protocol in the referenced document. Those physical properties marked with an asterisk and referenced as calculated were developed from other data on this sheet by Schroy. Values from laboratory work or literature are referenced as in the Table 1.1 References. Values not available from laboratory work or the literature were estimated using methods given by Reid et al. (1977), and are identified as RPS.

## References for Table 1.1


ADA Adams, W.J., and Blaine, K.M.. "A Water Solubility of 2,3,7,8-TCDD", Monsanto Co., St. Louis, Missouri, Dioxin 85 - 5th International Symposium on Chlorinated Dioxins and Related Compounds, Byreuth, FGR, September 16-19, 1985.

BRM Boer, F.P., van Remoortere, F.P., and Muelder, W.W. (1972). The preparation and structure of 2,3,7,8-tetrachloro-p-dioxin and 2,7-Dichloro-p-dioxin. Journal of the American Chemical Society, 94(3).

CAD Casarett, L.J., and Doull, J. (1980). Toxicology: The Basic Science of Poisons. 2nd Ed. Macmillan, New York.

CALC Calculation based on other physical properties. Activity coefficient based on water solubility. Theoretical oxygen demand based on molecular weight. Partition coefficient for air/water based on activity coefficient.

CDC Centers for Disease Control, U.S. Department of Health and Human Services, personal communication. (1982)

ETD Esposito, M.P., Teirnan, T.O., and Dryden, F.E. (1980). Dioxins. EPA-600/2-80-197. U.S. Environmental Protection Agency, Office of Research and Development, Washington, D.C.

IUPAC International Union of Pure and Applied Chemistry. (1979). Atomic weights of the elements 1977. In Pure and Applied Chemistry. 51:405-533.

KEN Kenaga, E.E. (1980). Correlation of bioconcentration factors of chemicals in aquatic and terrestrial organisms with their physical and chemical properties. Environmental Science and Technology, 14(5), 553-556.

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RPS Reid, R.C., Prausnitz, J.M. and Sherwood, T.K. (1977). The Properties of Gases and Liquids. 3rd Ed. McGraw-Hill, New York.

SHA Shaub, W.M. (1982). Estimated thermodynamic functions for some chlorinated benzenes, phenols, and dioxins. Thermochemica Acta, 58, 11-44.

SFT Seaton, W.H., Freedman, E., and Treweek, D.N. (1974). CHETAH - The ASTM Chemical Thermodynamic and Energy Release Evaluation Program. ASTM DS 51. American Society for Testing and Materials.

VA JRB Associates. (1980). Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins. Volume I. Analysis of Literature. Veterans Administration, Department of Medicine, Washington, D.C.

because the agents of concern are primarily rigid-ring systems. This approach will permit the estimation of Henry's Law Constant and distributive tendencies. Estimation of partitioning behavior across organic liquid/water, air/water, and organic liquid/air interfaces can then be made. This will aid estimates of mass transfer processes such as sorption/desorption, volatilization, diffusion/dispersion, and advection. These data are critical to understanding and ultimately controlling the human and environmental impact of these low volatility materials.

## 1.3 Transformation Processes

Important transformation processes considered by the group included photochemical processes, chemical transformations, biological processes, and surrogate parameters for combustion.

### 1.3.1 Photochemical Processes

As the dominant transformation process for TCDD in the environment, photolysis offers the most promise for degrading dioxins in air, on soil, and in water. Experiments by workshop participants and others have demonstrated that sunlight photolysis of TCDD in organic media, water, and on some surfaces may be rapid. Other studies have indicated that the transport of TCDD occurs slowly but measurably to the soil surface, where photolysis can occur either on the soil surface or in the vapor phase above it. TCDD can be introduced into the atmosphere from incinerators and other incomplete combustion processes and by volatilization from water. Sorption onto airborne particulates and subsequent photolysis are also possible. All of these degradation processes serve to reduce TCDD bioavailability in the environment.

Demonstrated degradation pathways for photolysis of TCDD involve both reduction and ring cleavage, but other pathways are possible, especially in water and air. Rate constants for sunlight photolysis in water and organic media are reasonably well known. However, little or no data exist for photolysis of TCDD in the vapor phase or for TCDD sorbed onto airborne particulates (e.g., fly ash, dust), or onto soil particles.

#### Research Needs

The primary research needs in this area include:

- measurements of the rate constants, quantum yields, and pathways of vapor-phase photolysis of TCDD in the solar range of light;
- similar measurements of TCDD sorbed onto airborne particulates, soil surfaces, and environmental adsorbents; and
- determination of major pathways for photolysis in solution.

Secondary research needs include similar measurements on other chlorinated dioxins and related compounds.

### 1.3.2 Chemical Transformations

Little work has been done on characterizing the chemical degradation reactions of dioxins or furans. These chemicals are somewhat refractory to certain reactions, as is the case with other highly halogenated aromatics. Few of these reactions have been studied adequately, except the reduction involving alkaline glycol.

Highly charged metal ions are capable of splitting aromatic ethers when a driving force is available through chelate ring formation. Thus, 1,2-dimethoxyanthraquione is selectively demethylated at the 1-position by Sn(IV) chloride to form the corresponding tin chelate. Such reactions suggest the possibility that tri- and tetravalent metal ions can assist in splitting the ether bridges of dioxins to form the very stable catecholate chelates of these metal ions. In addition, the loss of one chlorine atom from TCDD results in a marked reduction of toxicity. Cleavage of the oxygen linkages also produces a much less toxic product.

#### Research Needs

A study of chemical reactions of the dioxins, furans, and related compounds will provide information for exposure estimates and other methods of altering the toxicity of these compounds. The types of reactions that should be studied include:

- dechlorination by alkaline-glycol treatment;
- oxidation and reduction by various reagents and catalysts, including metal oxides;
- ether cleavage with various reagents, including highly charged metal ions;
- metal complexation and coordination; and
- other types of reactions that future research may indicate.

### 1.3.3 Biological Processes

Biological methods for TCDD degradation may offer significant economic advantages over other technologies. Despite the evident persistence of TCDD in soil, there are indications that it can be microbially detoxified. Because of its structure, the initial step in the microbial transformation of TCDD requires either hydroxylation by an oxygenase or a dechlorination reaction. Some microorganisms with a monooxygenase system have been shown to degrade TCDD by incidental metablism to a hydroxylated product. The rate of this transformation can be increased by facilitating cellular uptake and by using a suitable substrate to induce the necessary enzymes. The hydroxylated products formed are expected to be less toxic because they can be biologically conjugated and eliminated; they are also more water soluble and dispersible. Fungi and yeasts are known to have a broad range of monooxygenase enzymes, including some that attack polycyclic aromatic hydrocarbons (PAHs). Mammalian monooxygenases have been implicated in hydroxylation and dechlorination of TCDD, and a mammalian monooxygenase gene has been transferred to and

expressed in yeast. The possibility of reductive dehalogenation by microorganisms in anaerobic environments also exists.

**Research Needs**

Microbial degradation of TCDD in contaminated soil or sediment requires the establishment of microorganisms that: can survive and thrive in the necessary environments; uptake TCDD in low concentrations; and contain an oxygenase system that can dechlorinate or hydroxylate TCDD. Research approaches to obtaining such strains are to:

- screen and genetically modify bacteria, yeasts, and fungi that express monooxygenases;
- construct bacterial systems through a continuous culture selection procedure; and
- bioengineer yeasts or fungi for expression of suitable mammalian monooxygenase activities.

Parallel studies are required to facilitate or genetically enhance the uptake of TCDD. This may be accomplished by adding solvents or surfactants, or by using surfactant-producing species.

### 1.3.4 Surrogate Parameters for Combustion

There exist today a large number and variety of facilities utilizing numerous feedstocks and combustion processes that may emit TCDD in measurable concentrations. Present methods of measuring TCDD in stack emissions from combustion sources are extremely complex and prohibitively expensive. In addition, the length of time for stack sample analysis prevents immediate feedback to the system operator for controlling TCDD emissions. Present research in this area has been confined to drawing limited correlations between TCDD emission levels and regularly monitored combustion parameters.

**Research Needs**

A research effort is needed to determine if inexpensive measurements of real-time combustion processes can be correlated with TCDD emissions and can be useful in controlling TCDD emissions from combustion sources.

## 1.4 Transport Processes

The important transport processes considered by the group included sorption/desorption/volatilization, intermedia transport, and advection/diffusion/dispersion.

### 1.4.1 Sorption/Desorption/Volatilization

Considerable data are available to characterize the adsorption and partitioning of organic chemicals, particularly pesticides, aromatic hydrocarbons, and PCBs, on particulate matter derived from soils and sediments. This has led to a number of correlations for estimating adsorption by soils for chemicals whose adsorption has not been measured. Organic matter content is considered to be the factor controlling the extent of adsorption and has led to the use of the $K_{OC}$ (octanol/water coefficient) concept for estimating adsorption.

Soil/water partition coefficients ($K_d$) of $10^5$ ml·g$^{-1}$ have been calculated for TCDD, based on measured values for water solubility and estimated values for octanol/water partition coefficients. Apparent TCDD partition coefficients ranging from $10^4$ to $10^6$ have been estimated, utilizing leachate data from a few contaminated soils from Missouri and New Jersey.

No information is available on partitioning behavior with respect to TCDD on atmospheric particulates. However, it has been postulated that the binding of TCDD to fly ash during combustion is irreversible.

Considerable information has appeared in the literature on the application of soil/water and air/water partition coefficients (Henry's Law Constant) to the transport of organics to the surface of a soil column, where they will be subject to volatilization. Currently, the estimated partition coefficients for TCDD must be relied upon for determining the volatilization potential for dioxins.

**Research Needs**

The primary research needs in this area include:

- determining rates and extent of adsorption/desorption in soil and sediment systems as a function of organic matter and mineral content, either to validate or to reject the $K_{OC}$ concept for predicting partitioning;
- identifying the mechanisms influencing TCDD partitioning onto mineral surfaces that are characteristic of soils having low organic matter content;
- determining adsorption/desorption on atmospheric particulates as a function of organic matter, mineral, and water content;
- characterizing the vapor-phase desorption isotherms as a function of particulate (soil, sediment, or air) composition and water content; and
- identifying the factors that would alter the predicted compound behavior in soil/sediment systems. Factors that should be investigated include: the presence of strong acids and bases or high levels of dissolved organic matter in interstitial waters; the presence of co-solvents; the movement of microparticulates, organic colloids, and colloidal clays; and the influence of organic micelles (or emulsions).

### 1.4.2 Intermedia Transport

Theoretical kinetic analyses of TCDD interphase transport have received limited attention. Low volatility substances such as TCDD have enormous activity coefficients in water. In volatilizing from water, TCDD probably forms a liquid film (two-dimensional gas) on the water surface. Thus, its transport to the gas phase probably depends directly on its thermodynamic activity. Transport between other phases probably operates in more complex ways. No detailed analyses of these transport systems are available. The lack of essential validated physical and chemical data currently makes analyses of intermedia transport very difficult.

#### Research Needs

The mechanism for intermedia transport must be characterized to understand and control the impact of any specific chemical on the environment. The rates of transfer between media, the capacities of the media, and the mass transfer coefficients need to be defined. In some cases, the kinetic measurements have not been attempted because of the difficulty of monitoring the mechanism. Significant environmental transport parameters in each medium, (e.g., particulates, soils, and sediments) must be characterized in terms of impact on the mechanisms of the transport processes. Distribution of the specific chemicals on surfaces or on particles of different sizes must also be examined. All these parameters must be characterized for TCDD and all dioxins and furans.

### 1.4.3 Advection/Diffusion/Dispersion

Advection of a chemical in air, surface water, and interstitial water in groundwater systems is the movement of the chemical with the bulk movement of the air or water. In some environments, chemical phases also need to be considered, including two-phase flow (water/organics), suspended particulates, and colloids. Although characterizing the advection of vapors and dissolved chemicals in water is frequently difficult, predicting advection in a second phase presents a more serious problem that remains unresolved in many instances.

The state of the art for estimating rates of diffusion and dispersion was ranked at previous EPA workshops on exposure assessment as poor to fair, and current estimations of diffusion and dispersion rates for TCDD isomers were ranked as poor. In general, molecular diffusion rates are calculated using estimates of molecular diffusivities. Procedures for estimating molecular diffusivities in the air are the most accurate; procedures for estimating diffusivities in water and soils are less accurate.

In addition to estimation of diffusivities, other physical parameters must be either measured or estimated to calculate diffusion rates in soils and sediments. These parameters include void fraction of soils or sediment volumes and tortuosity of the diffusion path.

Dispersion of chemicals in air and surface waters results from the turbulent motion of the fluid. Dispersion rates in these media are functions of a variety of physical parameters such as wind or water velocity, and temperature and density

gradients. In addition to possible turbulent motion, dispersion may occur because of the heterogenous characteristics of solid phases. Consequently, dispersion in soils and, potentially, in sediments must take into account site-specific characteristics and scale factors.

### Research Needs

Calculations of the amount and rate of TCDD advected into, through, and out of each medium are required for both the vapor phase and TCDD sorbed to particulates. The need to improve abilities to characterize, measure, and predict advection in saturated and unsaturated soils, sediments (interstitial waters), and estuarine waters should receive the highest priority. Also, advection in two-phase flow must be characterized for these systems.

The rates and extent of the diffusion and dispersion processes for TCDD must be better characterized for saturated and unsaturated soils and sediment systems, including the two-phase flow. This also includes the development of better techniques for measuring the significant environmental factors that govern the process rates and extent, such as void fraction and soil temperature.

## 1.5 Modelling

For the transport and transformation of individual chemicals in air, water, and soil environments, many mathematical models are available to predict exposure profiles necessary for bioavailability estimates. Models offer a method to organize information on many different processes occurring simultaneously, and facilitate the interpretation of laboratory and field observations and the determination of rate-controlling steps. Models range from very simple, steady-state algorithms to very complex, process-oriented dynamic codes. Simple models are easy to use but are usually inappropriate for site-specific field situations. More comprehensive, complex models, although possibly more realistic, may contain variables for which data are not readily available or for which methods are inadequate or unavailable to measure magnitudes in time and space. Examples of this problem include measuring the water conductivity in soils and the spatial variability of dispersion coefficients in air and soils. However, judicious selection and use of appropriate models can provide the most reasonable approach for solving complex exposure problems.

### Research Needs

With regard to the use of complex models, there is a continuing need to develop more efficient numerical methods to solve coupled systems of nonlinear, partial differential equations that are stable and present solutions with low levels of numerical dispersion. To facilitate the development of realistic complex models, the efforts of the laboratory scientists, field researchers, and modellers must be closely coordinated. Without such coordination, inappropriate models may be developed and applied to field conditions to predict exposure concentrations from contamination episodes.

In addition, it is necessary to determine the conditions under which single chemical models can legitimately be used to predict the transport and transformation of mixtures. It is tacitly assumed that for contaminants with low solubilities, and even for most designated air pollutants, the concentrations in the transporting medium are so low that they act independently of one another. This assumption is certainly not true in a photochemical smog episode, and it remains an issue for which no clear criteria exist to determine the set of chemical properties or concentrations for which interactions are significant or negligible. Thus, models that address the issues of mixtures and their interactions are needed, particularly for dioxins and furans. Also, the application of models to the complexities of multiple-phase transport imposes an additional level of difficulty in developing meaningful numerical solution techniques.

## 1.6 Analytical Methodology For Analyses Of TCDD In Environmental And Human Samples

Analytical methodologies currently utilized by EPA for analyzing TCDD in environmental and human samples involve:

1) fortification of the sample with an isotopically labeled TCDD;

2) extraction with an organic solvent when analyzing soil, sediment, and water; or

3) saponification with alkali followed by solvent extraction when analyzing biologicals such as human tissue.

Interferences are removed by acid and base partitioning steps, followed by chromatographic cleanup on alumina and charcoal columns or high performance liquid chromatography. A portion of final concentrated extract is subject to isomer-specific analysis by capillary gas chromatography and mass spectrometry, using selected ion monitoring. The quantity of TCDD reported is corrected for recovery efficiency of the labeled standard in each sample.

This analytical methodology has focused on TCDD; however, it has also been extended for the quantitative determination of other dioxin isomers and polychorinated dibenzofurans. Several matrices have been analyzed, and their respective minimum detection limits (MDL) are listed in Table 1.2.

Rigorous quality assurance has been incorporated into the analytical methodology. Samples are analyzed in well-defined sets that include blanks, spiked matrices, duplicates, and blind samples. Some samples are exchanged and analyzed by outside laboratory collaboration. A panel consisting of scientists outside of EPA has been established to review analytical results before their release.

### Research Needs

Sufficient supplies of TCDD are needed for research, as well as for standards and reference samples for quality assurance and quality control.

Table 1.2

Minimum Detection Limits (MDL) of Selected Matrices[a]

| Matrix | MDL Range | | |
|---|---|---|---|
| Water | 0.008 | to | 1.0[b] |
| Human milk | 0.1 | to | 5 |
| Deer adipose muscle, liver, bone marrow | 0.4 | to | 5 |
| Human adipose, beef adipose, beef liver | 0.5 | to | 10 |
| Elk adipose | 1 | to | 5 |
| Pork adipose | 4 | to | 7 |
| Pottery clay | 4 | to | 7 |
| Dog adipose | 1 | to | 10 |
| Fish, herring gull tissue | 1 | to | 10 |
| Soil, sediment | 1 | to | 10 |
| Fly ash from coal-fired power plants | 1 | to | 10 |
| Fly ash and gas-phase effluents from municipal incinerators | 1 | to | 300 |
| Chemical disposal sites | 10 | to | 800 |
| Chemical products and processes | 20 | to | 800 |
| Chemical destruction processes | 20 | to | 800 |

a Prepared by A. Dupay and R. Harless.

b Based on 1000-g samples.

## Environmental Processes in Bioavailability Working Group

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# CHAPTER 2

# BIOAVAILABILITY IN ECOSYSTEMS

Co-chairpersons: Thomas Duke and Mark Harwell

## 2.1 Introduction

Chlorinated hydrocarbons, including dioxins, are found in terrestrial and aquatic ecosystems and are bioavailable to certain organisms. The bioavailability of these chemicals should be considered in a holistic manner, because ecosystems typically consist of dynamic assemblages of thousands of species existing within a complex and heterogeneous chemical and physical environment, with which they interact. Biological organisms control ecosystem processes of energy and material flow, and they modify the chemical and physical environment. Alternatively, the environment substantially affects the distribution, abundance, and diversity of these biota.

An important aspect of ecosystems is that they operate simultaneously on widely differing spatial, temporal, and structural scales. The focus may be on individuals, populations, and communities of species, or on integrative measures such as diversity, productivity, respiration, and decomposition. For our purpose here, the term ecosystem includes all of these aspects, and the term bioavailability means the exchanges between the environment and the biota, and exchanges from biota to other biota. In large part, this mutual interaction between the environment and biota focuses on the interface between chemicals in an abiotic phase and between chemicals within the biota. Exchange across this interface is the central element of bioavailability. The concept of bioavailability here includes both the dynamic and steady-state aspects.

Both the rates of exchange, such as the rate of dioxin uptake by plants from soils, and the ultimate (steady-state) levels of dioxin accumulated in biota are of interest, especially as represented by bioconcentration factors (e.g., the dioxin concentration in plant tissue divided by the concentration in the soil).

The ecosystem considerations for dioxin have two distinct facets: the effects of dioxin on the biota in the ecosystem, and the role of the ecosystem in mediating dioxin exposure to humans. The human exposure pathways represent a special case of the more general investigations of the fate and transport of dioxin within ecosystems. Routes that take dioxin from an abiotic phase into biotic material ingested by humans are worthy of careful attention; these are discussed in the following sections on aquatic and terrestrial ecosystems.

Effects on ecosystems begin with effects on individuals. These effects can be manifested as physiological responses, behavioral responses, or even death of

individual organisms. But translating effects on individuals to effects on a population is not a simple extrapolation. Effects on populations are influenced by the interactions of the individuals within the population and with other species, and also by the nature of the physicochemical environment. For example, compensatory mechanisms may decrease adverse effects on populations; conversely, differential sensitivity within life stages may result in greater effects on natural populations than would be predicted from laboratory bioassays on individuals.

Community-level effects involve an increase in complexity, where indirect effects may result when a population not directly exposed to dioxin in the biotic phase becomes indirectly exposed through food-web interactions. Community composition can be affected by indirect effects involving predator-prey interactions, changes in competitive relationships, and induced susceptibility to disease or parasites, among the many various possible interactions. In considering community compositional changes, particular species or groups of species may be identified as being especially important, whether for economic, aesthetic, or ecological reasons.

Finally, additional factors influence ecosystem process-level effects. For example, if different species perform the same functional roles, whole species can be lost or populations altered without changing ecosystem processes, because of such functional redundancy. Conversely, if fundamental ecosystem processes are affected, biological changes can be expected to occur in commmunity composition, which is dependent on those processes. Thus, in some instances, biological responses to toxic chemicals might be better understood by measuring ecosystem processes directly rather than by monitoring species composition and diversity.

To predict effects of dioxin on ecosystems and on humans, the transport and fate of dioxins in the environment must be understood. The bioavailability of dioxins to biota, exchanges among biota, and influences of organisms on the movement of dioxins within and across systems must be included. A conceptual model of exchanges of dioxins among ecosystem components appears in the next section. Subsequent sections address transport and fate in aquatic and terrestrial ecosystems, effects on biota (species and processes), and pathways to humans.

In these sections, three sets of topics were considered: 1) identification of ecosystem processes that are involved in routes, rates, and reservoirs of dioxins in aquatic and terrestrial ecosystems, sensitive to effects of dioxin contamination, and involved in biological decontamination processes; 2) identification of particular species and communities that are potentially affected by dioxins; and 3) the role of food chains and food webs in human exposure and risk.

Overlying all of these topics are issues of scale across time and space and issues of uncertainty. Scale issues include determining the spatial and temporal extent of exposure and effects, differentiating chronic versus acute exposures, and considering whether there is sufficient time for potential compensatory mechanisms to operate. Uncertainty follows from lack of information, spatial and temporal heterogeneity that can obscure effects, differences among species in sensitivity to direct effects, propagation of indirect effects, and unexpected consequences.

## 2.2 Exchanges Of Dioxin Among Ecosystem Components

### 2.2.1 Conceptual Model

The purpose of most ecosystem models is mathematically to describe complex ecosystem interactions among biotic and abiotic components. Once an appropriate model has been developed, it can be used to answer questions about higher-level processes, such as chemical transfers through the ecosystem. Information on both process rates and component concentrations is utilized. Mathematically, it becomes more difficult to develop and verify a model which increases in complexity from species to population to community level. At the ecosystem level, validation of models is difficult or impracticable.

To obtain a better understanding of the bioavailability of dioxins to both lower and higher forms of life, and movement from one component to another, and to identify areas of critical research needs, we have presented a food-web model applicable to both aquatic and terrestrial ecosystems (Figure 2.1). The conceptual model figuratively describes interactions and dioxin exchanges among abiotic and biotic components. The dioxin pools in a number of biotic components are shown, including the transfers among biotic compartments through feeding. Also shown is a general abiotic pool of dioxins. The open arrows represent the exchanges of dioxin among abiotic phases and each type of biota. Details can be added to this abiotic pool, making the conceptual model applicable to different types of ecosystems.

The model is generic; from it, calculations can be made based upon assumptions of the thermodynamics of the toxicant. We recognize that equilibrium conditions do not always exist in the environment; however, we believe this is a useful approach for calculating initial estimates of dioxin concentrations for some components. In general, the tendency for change is towards thermodynamic equilibrium. Thus, the bioavailability of dioxins to organisms can be evaluated, and the hazard or risk of compartmental concentrations can be assessed.

### 2.2.2 Research Needs

Research should be conducted to:

- measure concentrations of dioxins with time in organisms as a function of dose in food, water, and other sources for model production;
- use microcosms to verify models; and
- conduct a full-scale ecological study at a highly contaminated site. This should include field studies of fate, chronic effects, and ecological processes, with supporting laboratory studies, and studies of the mechanisms of effects.

## 2.3 Bioavailability: Aquatic Ecosystems

### 2.3.1 Introduction

The distribution, transport, and fate of TCDD and other dioxins and furans in aquatic ecosystems are governed by processes that are generally known from studies

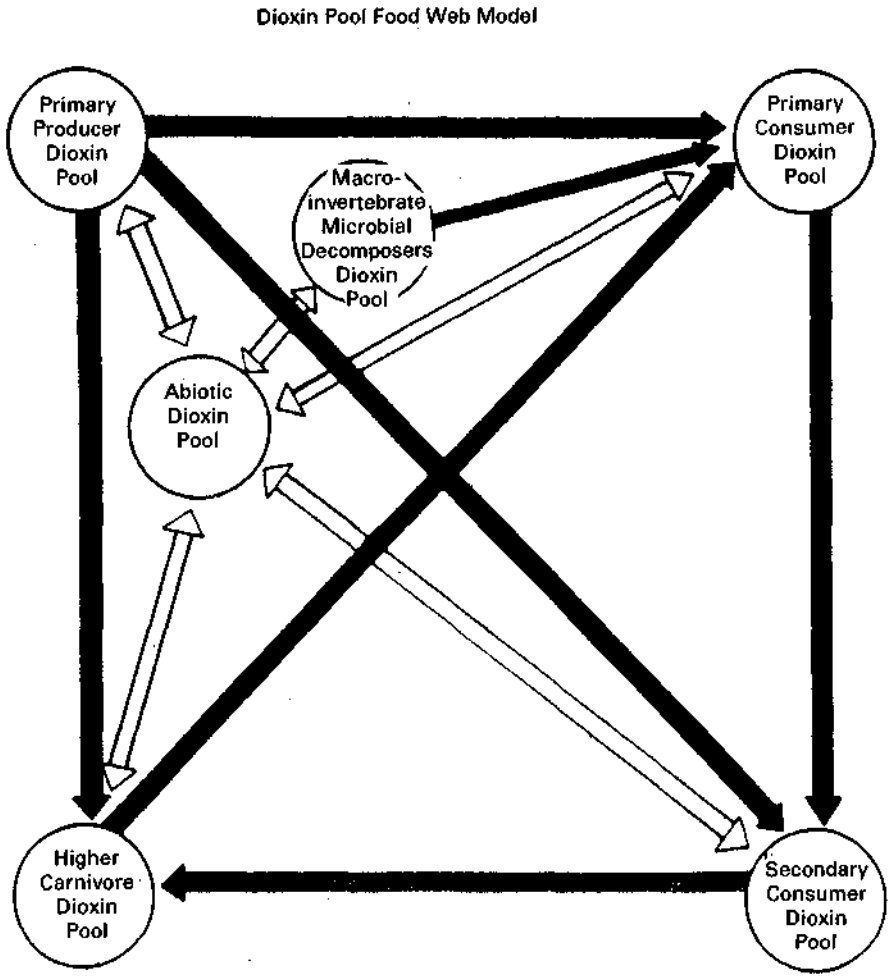


Figure 2.1 Dioxin pool food-web model. Solid arrows indicate abiotic dioxin flux by predation and feeding; open arrows indicate direct exchange between the abiotic and biotic components. This concept can be expanded to demonstrate dioxin pool exchange between two more foci webs of the ecosystem.

of other hydrophobic organochlorine compounds such as PCBs. All these compounds share an affinity for the carbonaceous component of suspended and settled sediment and for dissolved organic matter; these characteristics influence bioavailability. Less can be inferred from these studies when we attempt to predict biological effects of chlorinated dioxins and furans because of uncertainties that exist with regard to uptake, metabolism, and the toxic model of action of these compounds. For example, the selective bioconcentration of TCDD observed in fish exposed to mixtures of dioxin isomers has not been predicted on the basis of dioxin isomers' similar water solubilities.

Our ultimate research goal is to develop methods for predicting the bioavailability of dioxins and furans to aquatic organisms in different environmental settings on the basis of the physical and chemical properties of isomers, routes of exposure, water chemistry, sorbent interaction, and pharmacokinetics of uptake. Estimates of the potential environmental impacts of dioxins will be improved and strengthened if the dose received by organisms can be accurately predicted. From a human health perspective, prediction of the amount of contaminant accumulated by organisms can indicate whether unacceptable levels may be expected in animals consumed by humans. Development of this capability will thus aid in designing water quality criteria and in evaluating the environmental risks associated with existing contamination and with future releases.

### 2.3.2 Routes and Rates of Uptake, Metabolism, and Elimination

The bioavailability and accumulation of a contaminant depends on its physical and chemical form and the rates at which it is taken up, metabolized, and eliminated by organisms. Physicochemical partitioning within the aquatic environment exerts a major influence on bioavailability of dioxins because the rate at which a compound can be taken up by an organism will vary widely, depending on the physical matrix with which it is associated. By analogy with other organic compounds, dioxins dissolved in water are expected to exhibit a high rate of uptake. Contaminants associated with organic and inorganic particles, dissolved organic matter, or food appear to be less readily incorporated. The rates of dioxin uptake from different source compartments and the physical and biological factors that affect the rates of incorporation need to be examined quantitatively so that the total incorporation by organisms can be predicted.

Although dioxins, like many other organochlorine contaminants, do not appear to be readily biotransformed, the rates and pathways of detoxification by aquatic organisms need to be examined. Information on the pharmacodynamics of dioxin distribution among tissues within an organism is needed to understand the metabolic fate, the mechanisms of toxicity, and the accumulation in tissues that are consumed by humans. Development of correlations between tissue distribution of dioxins and molecular components of the tissue, such as lipid content, would be particularly relevant.

Rates of elimination of TCDD appear to be very low, although other TCDD isomers may be eliminated more rapidly. Because the body burden of dioxins accumulated by organisms will be largely determined by their elimination rates, it is

important to increase our knowledge about the rates and routes of elimination of dioxins.

The rates and routes of uptake, metabolism, and elimination of dioxins, and thus the body burden present at any time, will be affected by natural and human-induced changes in the environment. The effect on these processes, of environmental variables, such as temperature, salinity, water chemistry, and dissolved oxygen, as well as the effects of nutritional status of the organism must be understood if a predictive capability is to be achieved.

### 2.3.3 Effects of Dioxin on Ecosystem Processes

Toxic organics can alter ecosystem processes. Although there are no data directly implicating dioxins in altered ecosystem processes, there are sufficient toxicological data to warrant concern. From the known physical chemistry of dioxins, it is expected that dioxin effects on ecosystem processes will be similar to effects of other toxic organics for which data exist (e.g., PCBs and PAHs).

Productivity, both primary and secondary, is a fundamental process of ecosystems. Dioxin contamination may pose a risk to the balance of productivity. Should dioxins affect any functional group of organisms (e.g., phytoplankton, filter feeders, or carnivores), there could be a shift in the energy flow patterns that might be detrimental to the overall balance of the ecosystem.

At the ecosystem level, the processes most sensitive to dioxin toxicity would likely be alterations of population behavior, fecundity, immunological resistance, and other life-history characteristics. However, the classic approach to community structure analysis is too coarse a measure. By the time parameters such as diversity are affected, the system is usually heavily contaminated.

There are insufficient aquatic field data on effects of dioxins. A data base needs to be developed from which the long-term consequences of dioxins in the environment can be evaluated. Research should focus on the key ecosystem processes described above.

### 2.3.4 Biological Decontamination Processes

Mechanisms to eliminate dioxins from ecosystems may have both biological and physical components. Biologically, microorganisms have the potential to degrade dioxins. Physically, photooxidation may be important in aquatic environments, but the removal of dioxins from the biologically active zone by sediment accumulation processes and burial is likely to be more important. Because dioxins are associated with fine-grained sediments, the transport and long-term fate of dioxins will be mediated by sediment transport processes. We also need to understand the dynamics of sediment transport as a mechanism for remobilization.

### 2.3.5 Biological Effects

Toxic effects of dioxins and furans in actual aquatic ecosystems have been studied in only a few instances. Factors complicating such studies include the virtual

absence of useful exposure data, particularly for water concentrations, the presence of complex mixtures of many organochlorine compounds, the nonspecific symptomology, the slow mode of action, and the levels of accumulation.

Fish-eating birds can accumulate TCDD and related isomers. Reproductive effects, including embryotoxicity and teratogenicity, are consistent with early research on the chicken and the putative agent in chick edema disease, hexachlorodibenzodioxin (1,2,3,7,8,9-HCDD). While previous studies on Lake Ontario herring gulls are now artifactual, unpublished research on the Forster's tern on Lake Michigan show continuing reproductive problems consistent with the known effects of these compounds.

The available data describing TCDD toxicity to aquatic organisms are limited to fish. Laboratory exposures of fish to TCDD that have been reported can only be used for a gross estimate of toxic effects. No information exists on the toxicity of other dioxin or furan isomers. In separate studies, northern pike (eyed eggs) and rainbow trout (juveniles) were exposed for four days to a range of static TCDD concentrations and held for depuration in noncontaminated well water. These studies indicate that TCDD is a slow-acting toxicant. However, the mode of toxicity appears to be different than for most other neutral lipophilic organic chemicals. It is not clear whether short-term exposures can ultimately produce the same dose-response relationships as continuous exposure to the same or lower levels over longer periods of time. The mode of action of TCDD toxicity in aquatic organisms is unknown.

Traditional methods for assessing acute toxicity, such as the 96-hour $LD_{50}$, are not useful in dioxin hazard evaluations. The available data are insufficient to gauge the magnitude of variability in interspecies sensitivity, although this may be quite large, as is the case for mammalian toxicity studies. At this time, a no-effect-concentration cannot be determined. Growth and reproduction have not been investigated for fish or invertebrates exposed to trace concentrations of TCDD for sufficient periods of time to allow steady-state concentrations to be reached in tissues. Bioassays performed with complex mixtures of dioxins, furans, and other organochlorine compounds produce toxic effects that indicate additive and possible synergistic interactions.

The toxicity of TCDD associated with suspended or settled sediments has not been determined. Water TCDD concentrations resulting from partioning with sediments may affect toxicity, especially if organism uptake is primarily via the gills. The ingestion of contaminated sediments, particularly by bottom-feeding fish and benthic organisms, presents a potentially important alternate route for uptake and consequent toxic effects. Bioassay systems adequate for long-term, controlled exposure of aquatic organisms to suspended and settled sediments are needed.

### 2.3.6 Role of Food Chains in Human Exposure

Aquatic organisms and fish-eating avians may accumulate dioxins and related compounds to levels of concern relative to both toxic effects and risks to human consumers of the organisms. However, a comprehensive understanding of dioxins that would allow the prediction of body burdens from exposure data has not yet been

achieved. Microcosm studies have provided estimates for bioconcentration factors (BCFs) for aquatic plants and animals; however, measurement of steady-state BCFs and those concentrations that may be achieved in nature have not been undertaken. Relationships between sediment concentrations and fish tissue concentrations are open to interpretation. Data suggest that fat or fat content of individual tissues may be an important determinant of bioconcentration in aquatic species. In summarizing the uncertainties related to body burdens in aquatic organisms, it appears that age, size, species, feeding relationships, and fat content are key considerations from a biological standpoint. Abiotic factors probably include: sediment transport and availability; characteristics such as particle size, organic content, and general complexing ability by organic compounds; and solvents as dissolution agents.

Sufficient information is available to establish the bioavailability and bioconcentration of TCDD and related compounds in salmonids and other species in the Great Lakes, in rivers and ditches that drain dumps, and in fields sprayed with 2,4,5-T. Knowledge of dioxin kinetics is much more sketchy concerning estuarine and marine species. Fish, snapping turtles, and fish-eating birds have been characterized in individual situations, but there is little understanding of the potential for biomagnification along food chains within a contaminated ecosystem. Because biomagnification is associated with orders-of-magnitude increases across biotic media boundaries, understanding the potential for biomagnification can be best determined by placing special emphasis on birds and mammals feeding on aquatic organisms.

### 2.3.7 Research Needs

The key area to be addressed in future research is a better understanding of factors controlling bioaccumulation. In addition to laboratory research on individual aspects such as fat content and partition coefficients, full abiotic/biotic food-chain research should be conducted to characterize contaminated areas. Areas differing in the relative dominance of perceived factors affecting food-chain transfer of dioxins and related compounds should be studied. To understand and develop a total human exposure model and institute risk assessments, aquatic food-chain influences (e.g., fish, turtles, crayfish, and waterfowl) need to be integrated with terrestrial wildlife concentrations, domestic food intake, and occupational/ambient exposures to determine adequately the primary pathways to humans.

Research should be conducted to:

- develop the capability to predict dioxin levels in tissues (particularly in organisms that constitute human food chains) as a function of environmental conditions;
- develop data for understanding the mechanisms of toxicity and the factors responsible for differential toxicity among species; and
- determine the nature and extent of disruption caused by dioxins in aquatic communities and the mechanisms by which they are caused.

## 2.4 Bioavailability: Terrestrial Ecosystems

### 2.4.1 Introduction

Few acute and chronic toxicity studies have been conducted to study TCDD effects in the field. The few field studies conducted on wildlife that are reported in the literature involve sampling trophic levels at contaminated sites and determining TCDD concentrations. Very few laboratory studies have been conducted to study the acute and chronic toxicity of TCDD to wildlife as well as effects on ecosystem processes. The limited data that are available from controlled laboratory and field studies show that TCDD bioaccumulates in terrestrial wildlife up to about 25-fold and that bioconcentration among trophic levels does not occur to any significant extent. In areas containing high concentrations of TCDD, studies are needed concerning TCDD bioaccumulation, bioconcentration in trophic levels, and ecosystem process effects. In isolated cases, some risk to humans could occur from food animals that have direct access to contaminated soils. The risk is most significant when individuals consume their own farm-raised products. Risk to the general public would be smaller because of dilution through marketing channels and diversity of dietary sources.

The major routes of contamination in terrestrial ecosystems are likely to be the movement of dioxins from soil to animals and from the atmosphere to plants. Liver and adipose tissues are the most likely reservoirs for dioxins in animals, and those in intimate soil contact harbor the highest dioxin concentrations. Assuming that susceptibility will be largely a function of exposure, those animals ingesting or inhabiting soil are the most likely to be affected by TCDD. This includes domestic animals or wildlife that eat soil along with food or grooming, as well as burrowing animals such as groundhogs, rodents, and rabbits. Soil-dwelling micro- and macroinvertebrates are also likely to receive high exposures.

### 2.4.2 Degradation of TCDD in Soil

The major processes of TCDD removal from soil are photodegradation and volatilization. It is generally agreed that microbial degradation of TCDD occurs to a very limited extent. Preliminary results of microbial degradation studies underway in Missouri indicate that microbial degradation occurs, but it is too early to draw firm conclusions. Refer to Chapter 1 of this report, Environmental Processes in Bioavailability, for additional information on this subject.

### 2.4.3 Bioconcentration in Wildlife from Soil

Whole-body and tissue concentrations of TCDD have been measured in a variety of wildlife species under conditions of chronic field exposure. The highest concentrations of TCDD are generally found in the liver and adipose tissues. Although dioxin concentrations may be influenced by factors such as trophic level, fat content, physiological state, and sex of the organism, the primary factor influencing uptake by wildlife appears to be the degree of contact with contaminated soil. In earthworms, which continually consume and contact soil, a direct linear correlation has been shown between body burdens of TCDD and soil concentrations. Despite reported body

burdens of TCDD in numerous organisms, no studies have definitively shown either population or community effects.

Unlike aquatic animals, terrestrial animals do not concentrate TCDD to a considerable extent. BCFs are generally around 25 or less. The highest BCF reported is 42, found in earthworms in Seveso, Italy. Interestingly, absolute concentrations of TCDD in aquatic animals have not exceeded those found in terrestrial animals despite the high propensity for movement from the water column into aquatic animals. It should be noted that BCFs for aquatic organisms usually describe the partitioning of dioxins between water and organisms, whereas BCFs for terrestrial animals usually describe the partitioning between soil and organisms that may not be in constant contact with soil.

There may be potential human food-chain exposure from wild terrestrial birds, such as wild turkey, pheasant, quail, and grouse, but no data exist to substantiate whether TCDD and related compounds (e.g., furans) exist in these species. Turkeys seem to be more sensitive to contaminants such as PCBs than the other species. However, relative sensitivities among species may be important to humans because wild birds may continue to accumulate concentrations of dioxins until consumed for food.

### 2.4.4 Movement through Soil to Food Animals to Humans

The major route of potential TCDD exposure to farm animals is by direct ingestion of soil. Intake of soil by grazing cattle and sheep is inversely related to the amount of available forage and may range from 2 to 15% of dry matter intake. Cattle may also consume soil at 2 to 4% of dry matter intake when confined to lots with no vegetation. Pigs consume 2 to 3 times as much soil as cattle. Data are not available for soil consumption by poultry with access to soil.

Monitoring data show a general correlation between herbicide application rates and TCDD levels in cattle. It has been suggested that BCFs for TCDD from soil to mammals range from 2 to 25. Field experience with the chemically related polybrominated biphenyls suggests that this is a reasonable conclusion for nonlactating ruminants such as cattle and sheep. This factor is slightly lower for lactating cattle because of the secretion losses through milk. BCFs are several times higher in pigs because of higher soil consumption. No BCFs are available for poultry.

TCDD is known to be highly toxic to domestic poultry, but essentially nothing is known regarding the quantitative aspects of dioxin interaction with these birds, particularly as related to potential metabolic pathways and residue retention by edible tissues or secretion into eggs. However, because of the highly controlled environment in which most commercial poultry is raised, soil contamination by dioxins is unlikely to result in significant concentrations in commercial poultry. In barnyard poultry, exposure at dioxin-contaminated sites is certainly possible, and limited studies suggest that contamination of meat (and presumably eggs) would result. There are no data to indicate what levels of dioxin residues in poultry meat or eggs would be expected from a given dietary intake level.

Given the nature of the presently known and likely to be discovered dioxin-contaminated terrestrial sites, the major potential for human dietary exposure to dioxin residues would probably occur through the consumption of meat or milk from farm animals held on contaminated sites. A number of available studies clearly indicate that exposure of farm animals, particularly cattle, to dietary dioxins will result in residue retention by edible tissues and secretion into milk.

Studies with the higher chlorinated dioxins suggest that in livestock, a limited degree of bioconcentration in tissues over dietary levels may occur. But, if bioconcentration occurs with TCDD, it may be considerably less. The available data on dioxin interactions with both lactating and beef cattle appear to be only marginally definitive with respect to their value in predicting residue levels that would occur in meat or milk as a result of specific levels of dietary exposure. Lactating cattle fed up to 500 ppt dietary TCDD resulted in milk levels of approximately 100 ppt, although 24 ppt dietary TCDD to beef cattle gave up to 100 ppt in fat and 10 ppt in liver. Studies have demonstrated that normal cooking processes do not generally reduce dioxin levels present in raw meats.

### 2.4.5 Movement through Soil to Plants

TCDD can translocate through plants; however, uptake from soil is generally very small, with an extremely small accumulation of dioxin into fruits and seeds. In field studies, contamination of aboveground plant parts has often been attributed to contaminated dust.

Dioxin binds to organic surfaces, including plant roots, and in the bound form is unavailable for absorption and translocation. Concentrations in fleshy roots at the root surface typically are similar to soil concentrations, with a sharp decrease toward the root center.

Uptake from solution and translocation into aboveground plant tissues occurs at rates that are easily measured and would be of concern under some conditions. Concentrations in soybean and oat leaves have been shown to be five and ten times (plant dry weight) the solution concentration after one day of exposure.

A possible contradiction between field studies and some laboratory uptake studies probably results from imprecise descriptions of the root/soil solution interface. In soil, dioxin is normally bound to particles and is therefore unavailable for uptake. Even binding to exterior root surfaces makes dioxin unavailable for uptake. However, when dioxin is in solution at the exterior root surface, uptake and translocation occur. Therefore, conditions that change dioxin solubility in soil may facilitate plant uptake.

There is no evidence in the scientific literature of plants being affected by dioxin, even at the highest levels of contamination studied. However, specific studies to examine phytotoxicity have not been done.

### 2.4.6 Research Needs

Research should be conducted to:

- evaluate the chemical and biological characteristics of residue from experimental incineration projects and apply the results to risk assessment;
- identify the mechanisms by which TCDD in bound forms is released in the gut and taken up by lactating and food animals; and
- determine the effects of soil organisms and plant roots on vertical transport and bioavailability of TCDD.

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# CHAPTER 3

# BIOAVAILABILITY TO HUMANS

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## 3.1 Introduction

This work has focused on bioavailability to humans, which refers to those characteristics of the toxicant (e.g., its form, route, matrix, and concentration) and the host that determine the internal biologically active dose. Risks may be inaccurately estimated in the absence of knowledge about factors determining bioavailability, even when exposure is relatively well defined. Clearly, matrix and route effects are likely to be significant. However, human responses and risk are also influenced by exposure and by differences in the sensitivity of target sites of action. To consider bioavailability adequately, exposure and toxic response must also be examined.

TCDD was the main concern of this report. The biological effects of TCDD have been more extensively studied than any other chlorinated dibenzodioxin or dibenzofuran. However, because many isomers of dioxin are usually found at the same sites, the possible influence of other isomers of dioxin on the bioavailability of the TCDD isomer is well recognized, and workshop discussions could readily be applied to these other dioxin isomers as well. Additionally, dibenzofuran isomers are often found in the same sites as the dioxins, and the furans could easily influence the bioavailability of TCDD and the other dioxin isomers. Because the furans and dioxins have very similar toxic end points, it was recognized that the following discussion would apply to tetrachloro-, pentachloro-, hexachloro-, and heptachloro- dioxin and furan isomers.

Bioavailability to humans, as the host organisms, has two aspects:

1) the uptake of chemicals from environmental matrices into the host and the interactions with critical receptors and tissues within the host; and

2) the subsequent distribution, redistribution, or mobilization within the host. Mobilization is a means of internal in vivo bioavailability that could be beneficial (by promoting excretion) or detrimental (by increasing exposure to critical organs).

These two aspects of bioavailability to humans served as the definition of bioavailability for this workshop group. Additionally, it was recognized that bioavailability could be an index of the potential for incorporation into humans.

## 3.2 Bioavailability Of TCDD To Humans From Environmental Matrices

### 3.2.1 General Properties of TCDD and Matrices

Physical and chemical properties of TCDD that should be considered include partition coefficients, vapor pressure, lipid coefficients, and solubilities, which have been discussed in Chapter 1.

Matrix types and characteristics that should be considered include soil, fly ash, aerosols, and solutions. A recent finding is that the length of time the TCDD is bound to soil may be critical for the subsequent extraction of TCDD from the soil, in that the longer the time TCDD is bound to the soil, the harder it is to extract TCDD. Various soil types result in distinctly different strengths of chemical binding with TCDD. Bioavailability is primarily dependent on the binding of TCDD to different matrices.

### 3.2.2 Research Needs

Matrices of various composition with known TCDD concentrations should be used to determine the bioavailability of TCDD by using the same species and toxicologic end points. Soil should be considered as a priority matrix because it is the most common one to which humans are exposed. Contaminated fly ash or respirable particles should be studied to determine their TCDD bioavailability to humans. A range of concentrations should be utilized, because the bioavailability of TCDD may differ at differing concentration levels.

## 3.3 In Vivo Bioavailability

### 3.3.1 Mobilization and Redistribution

In vivo bioavailability is a measure of the amount of TCDD that is at the target organs, cells, or cellular constituents. In addition to the TCDD that is available from environmental matrices, TCDD is also bioavailable from TCDD mobilization or redistribution within the host in specific tissues, organs, or cells. After TCDD enters the host from an environmental source, it is distributed to target organs or storage depots. However, TCDD can be mobilized from depots and redistributed to target organs or other depots, producing an in vivo bioavailability that should be recognized. Although there are no data on the mobilization of TCDD in humans, knowledge of the bioavailability of TCDD by mobilization has been documented in other animals. This aspect of bioavailability is extremely important because any TCDD stored in the human body in the adipose or other tissue is always a source that could be mobilized under a number of conditions and has the potential to produce toxicity in the host. The determination of the end points of toxicity and quantification of the degree of toxicity will be dependent on the internal distribution of TCDD.

It is important to know how host factors such as possible pregnancy, age, nutritional status, and prior exposure influence the in vivo bioavailability by mobilization and redistribution of TCDD, with the possibility of altered end points or

altered degree of toxicity. Moreover, several critical organs and cellular targets are likely, so that all of the implications of redistribution are not known. Nevertheless, it is important to enhance excretion, directly or by redistribution, to limit distribution or redistribution to such sensitive tissues as fetuses and gonads, and to prevent secondary exposure via breast milk.

### 3.3.2 Research Needs

There are very few data on animals or humans in which the concentration of TCDD from an in vivo bioavailable source is known. Studies and techniques are needed for the determination of TCDD from a primary exposure and from a secondary exposure through mobilization and redistribution.

The determination of the TCDD body burden in humans is needed, with adipose tissue being the most important tissue to be examined. This would permit a direct comparison to the other halogenated hydrocarbons and dioxin and furan isomers that would provide a background profile of the extent of contamination of these compounds in the human population.

Additional studies should determine the residue of TCDD in other organs of humans that might determine TCDD target organs as well as the possible mobilization and redistribution of TCDD. This would also suggest the possible metabolic pathways and/or secretion or excretion patterns in humans.

To perform many of the studies, there is a need to develop and validate assays for TCDD that are rapid and economical, either in vivo or in vitro, and that can be used to determine the concentration of the TCDD in the various organs of the body. This would be necessary for studies to determine mobilization and redistribution of TCDD.

Analytical chemical methods for the direct measurement of TCDD are available for fat and for breast milk analyses (see Table 1.1 in Chapter 1). These methods should be applicable to other organs, some of which can be assayed by biopsy. Biopsies would permit the determination of TCDD in various organs which could be related to the microscopic examination of the biopsy.

Toxicity end points could be used to estimate the bioavailability of TCDD, but they lack specificity. It is well established that TCDD produces chloracne in humans and some animals. Although this response is not specific for TCDD, the assay could be a sensitive indicator of TCDD. Enzyme changes and alteration of porphyrin metabolism could be explored as indicators of TCDD bioavailability, although they also lack specificity. Extracts of various matrices could be assayed for TCDD bioavailability by indirect in vitro methods, such as induction of rat hepatocyte aryl hydrocarbon hydroxylase (AHH) activity, human lymphocyte AHH activity, and porphyrin changes in human fibroblasts, although there are no data on the alteration of porphyrin metabolism in humans as seen in other animals. These indirect methods are not specific for TCDD, and it should be recognized that other dioxins and furans can, and do, affect these end points, confounding the results. Specificity might be obtained by methods that are under development for estimating the concentration of TCDD using radioimmunoassay and monoclonal antibody techniques.

## 3.4 Host Factors Influencing Bioavailability

Many host factors can modulate the bioavailability of TCDD with an increase or decease of availability. Because there are many host factors, only some of the well known factors will be addressed.

### 3.4.1 Dietary Factors

Dietary consumption patterns influence exposure and may also influence bioavailability by affecting absorption and rate of retention in the gastrointestinal tract. The nutritional status of the host in terms of deficiencies, malnutrition, and specific diets (e.g., high or low fat) will influence bioavailability by increased or decreased uptake. Body fat content will have a major effect on distribution and mobilization.

### 3.4.2 Genetic Differences

It is well known that genetic differences can influence absorption, biotransformation, receptor interaction, and excretion of many toxic agents in numerous species. However, very little is known about these factors in humans. Although few data are available, it is recognized that genetic differences could be a major factor determining the variability of bioavailability in humans and subsequent toxic manifestations. Studies should be undertaken with responsive and nonresponsive mice to indicate a possible range of effects.

### 3.4.3 Age

Both behavioral and physiological characteristics related to age influence bioavailability. Factors such as dermal penetrability and gastrointestinal absorption change with age. Also, there is evidence from animal studies for oncogenetic development of cellular receptors for TCDD.

### 3.4.4 Concomitant Exposures

TCDD is similar to other chlorinated hydrocarbons in its manifestation of toxicity. Concurrent exposures to other chlorinated hydrocarbons as well as furans and other dioxin isomers may influence the bioavailability of TCDD by competition, inhibition, or enhancement. However, very few data are available on this topic relating to humans.

### 3.4.5 Exposure History and Other Factors

Prior exposure to organic chemicals may enhance or reduce the uptake and retention of TCDD, thus influencing the bioavailability.

Other host factors to be considered are behavior, lifestyle, and health and disease states. Data are insufficient to warrant high priority consideration of these factors. However, information from occupational studies may assist in reevaluating the importance of these factors.

### 3.4.6 Research Needs

Adequate consideration of research needs in the area of host factors affecting bioavailability is hampered by a lack of knowledge regarding critical target organs and the best choice of an animal model for human toxicity. The appropriate animal species to use as a model for studying host factors, tissue distribution, and mobilization from body stores is needed because data show that the tissue distribution of TCDD differs in monkeys and rodents (see discussion in Section 3.5). Many end points of toxicity could be studied; however, the critical end point in TCDD toxicity is not known. Some end points that should be considered are: elevation of blood lipids, increased production of porphyrins, impaired immune response, peripheral neuropathies, and dermal disorders such as chloracne. Other biochemical markers need to be determined, especially those specific to TCDD; however, these would also most likely be indicative of the other dioxins and furans. Additionally, the extent to which data on other dioxin and furan isomers can be applied to TCDD should be evaluated.

## 3.5 Interspecies Differences Affecting Bioavailability

Data derived directly from in vivo studies of TCDD bioavailability in humans would obviously be most useful in addressing the issue of bioavailability. However, for ethical and other reasons, it is likely that most of the data on bioavailability will, of necessity, be derived from in vivo studies using laboratory animals as surrogate testing species.

Therefore, it was deemed imperative that these anticipated animal studies on bioavailability be planned, conducted, interpreted, and extrapolated to humans in a scientifically appropriate manner that accommodates all the information on the interspecies differences affecting bioavailability. These differences can be delineated into two groups: the more general conceptual interspecies differences applicable to many xenobiotics, and the more specific interspecies differences of particular importance in evaluating the bioavailability of TCDD and other halogenated dioxins and furans.

The interspecies differences affecting bioavailability by the three principal routes of exposure (dermal, ingestion, and inhalation) would include, but are not limited to, the following variables among humans and the various laboratory animal species likely to be used in the in vivo studies of bioavailability.

### 3.5.1 Dermal Route

The dermal route of exposure to TCDD provides a direct mechanism for absorption of the toxicant. This exposure can result from direct contact with contaminated soil or through air transport of dust or fly ash.

#### 3.5.1.1 Dermal Studies

Anatomical and physiological differences among humans and various laboratory animal species would include factors such as the presence or absence of an

integumentary hair coat, the thickness of the hair coat, the thickness of the epidermis and dermis, the presence or absence of integumentary adnexal structures such as sebaceous and sweat glands, the comparative aspects of the subcutaneous fat and vasculature and lymphatics, the comparative ratios of skin surface area to body weight, the comparative enzymatic capabilities of the dermis, and the comparative potential for binding to plasma proteins after dermal absorption.

**3.5.1.2** Research Needs

Evaluation of the suitability of various in vivo and in vitro models is needed for predicting dermal absorption of TCDD. Dermal uptake of TCDD should be examined in several species in vivo. Direct absorption from various matrices, such as soil and fly ash, should be examined. Species that might be considered include pigs (neonatal skin), rats, guinea pigs, and mice, including dermal uptake by both responsive and nonresponsive strains of mice. Uptake by various species in vivo should be compared to transport in at least one in vitro model using skin explants from the same species as well as uptake in human skin culture. Species differences in uptake in vitro should be compared with species differences in vivo to determine whether the in vitro model is predictive of the in vivo data and to determine in which species dermal absorption most closely resembles absorption by human skin.

### 3.5.2 Oral Route (Ingestion)

In a second type of exposure, ingestion, bioavailability is a function of whether TCDD intake is from eating contaminated foods or from exposure to TCDD-contaminated soil or dust. If TCDD-contaminated food is consumed, bioavailability becomes analogous to bioaccumulation.

**3.5.2.1** Oral Studies

Comparative studies of bioavailability using various laboratory animal species as surrogates for humans should consider the following variables: interspecies dietary patterns (herbivorous, carnivorous, or omnivorous), anatomical differences such as the presence or absence of cecum, comparative transit times via the gut, comparative aspects of biliary salt production and pancreatic enzyme production, comparative differences in pH within the gut, comparative aspects of enterohepatic circulation and gut flora, and intestional vasculature and lymphatics.

**3.5.2.2** Research Needs

In bioavailability studies of TCDD, feeding contaminated soils to various laboratory animals has produced substantial differences in response. Thus, the differences in bioavailability that have been identified warrant further studies. Some of these further studies should use variations of the more conventional in vivo test procedures that have been utilized in bioaccumulation studies with certain laboratory species such a guinea pigs and rats.

Other types of studies that should be done, the results of which could lead to generalizations that can be modeled, include in vitro gut sack and substituted

gastrointestinal content studies as a means to estimate release of TCDD from matrices. Gut sack studies allow the investigator to examine the role of different areas of the intestinal tract in absorption and transport. This model is easily adaptable to several animal species, including the human digestive tract from surgical specimens. The human specimens would be necessary to extrapolate data from animals to humans.

Substituted gastrointestinal content studies are currently carried out by the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture to determine the release of dislodgeable residue of pesticides and the release of active ingredients from medications, particularly generic equivalents. This approach could be coupled with high-resolution analytical techniques to estimate the effect of the digestive process (time, pH, and volume) on dislodging TCDD from matrices.

The monitoring of the human diet by the FDA should be sufficient to estimate the bioavailability of TCDD from diet. However, special situations may need direct study, such as people on a high-fat diet, people growing gardens next to dump sites, or children ingesting dirt.

### 3.5.3 Inhalation Route

Municipal waste incinerators have been well characterized as being potentially chronic, dispersive sources of low levels (parts per trillion) of chlorinated dioxin isomers into the atmosphere. At some time following release from incinerator stacks, those isomers not already adsorbed or absorbed to particulates will become bound to particulates as the compounds reach sublimation. Therefore, human exposure can be predicted to occur by inhaling TCDD-bound particulates into the respiratory tract. Bioavailability would then become a function of particle size, the chemical nature of the particulate, the distribution of TCDD in relation to particle size, the dynamics of particle-size retention in the lungs, and the action of the lungs in dissolving, digesting, or extracting TCDD from the particles.

#### 3.5.3.1 Inhalation Studies

Inhalation of TCDD from environmental matrices should be studied in at least a rodent model. One such study should determine the bioavailability of TCDD in rats exposed to dusts generated from specific sites or matrices. The matrices should be selected to represent extreme conditions of absorption, so that models can be built to assess human risk without testing every contaminated site or matrix.

The dusts (particulates) should be generated by a dust feeder that allows particle sizing, such as the Wright Dust Feeder. The dust should be analyzed prior to animal exposure. The analysis should include the compounds present, the type of matrix, and the composition of the matrix. After nose-only exposure, the biochemical markers and toxicity indicators should be determined. A major question to address is which compounds are retained compared to compounds in the original sample. The nose-only inhalation procedure eliminates the possibilities of dermal deposition and absorption, as well as oral ingestion from grooming.

#### 3.5.3.2 Research Needs

In view of the predominant concern regarding exposure to particulates, anatomical and physiological differences should be addressed. Anatomical differences among humans and the various laboratory animal species should be examined in regard to the upper respiratory tract, the bronchiolar tree, the alveoli, and the pulmonary vasculature and lymphatics.

Physiological differences would include respiratory volume, respiratory rate, particulate sedimentation rates for the upper and lower respiratory tracts, comparative aspects of clearance via mucociliary apparatus, retention time, and the ultimate fate for particulates that do reach the alveoli.

When designing studies of bioavailability in laboratory animals, consideration of these general issues should be supplemented by more specific issues of special importance for the chlorinated dioxins and furans that are discussed in the following two sections.

## 3.6 Pharmacokinetics And Structure-Activity Relationships

Absorption, distribution, and excretion of dioxins and furans have been studied in a number of species. These compounds were found principally in the liver and fat of all species examined. Differences among species in metabolism or distribution do not appear to account for differences in species sensitivity.

### 3.6.1 Pharmacokinetic Studies

The most toxic isomer of dioxins and furans is substituted in all four lateral 2, 3, 7, and 8 positions; however, extensive in vitro and in vivo quantitative structure-activity relationships have not been fully developed. This information could readily be used to predict the toxic end points and human toxicity of isomers of this large class of toxic environmental agents. The few structure-activity relationships of dioxin isomers indicate that TCDD is the most toxic compound, with the other isomers being less toxic. Estimating the toxicity of mixtures of these various dioxins and furans is not possible, simply because too little is known about the toxicity of the individual compounds or the possible interaction of the compounds.

### 3.6.2 Research Needs

The areas that should be studied include:

- the effects of structure on the biologic and toxic activities of dioxins and furans;
- the development and validation of quantitative in vitro bioassays that can be used to predict in vivo effects of dioxins and furans;
- a study of the in vivo interactive effects of dioxins and furans and the determination of additive, synergistic, and antagonistic effects;

- a study of dioxin and furan isomers and the effects of structure on pharmacokinetics in exposed animals;
- the role of interactive effects on the pharmacodynamics of mixtures; and
- the effects of receptor level modulation (e.g., by PCBs and PBBs) on the toxicity of individual dioxins, furans, and their mixtures.

## 3.7 Epidemiology

When reviewing the results of animals studies, it is easy to look at only one compound, TCDD. However, when reviewing epidemiological data, it is extremely difficult to deal with only one compound, because most exposure groups have been exposed to a mixture of compounds or isomers. For this reason, we feel that the focus of dioxin research must address a number of compounds, including dibenzodioxin, dibenzofuran isomers, and halogenated hydrocarbons.

### 3.7.1 Epidemiological Studies

There have been a large number of animal studies on the adverse biological effects of TCDD exposure such as hepatotoxicity, porphyria, dermal changes, teratogenicity (e.g., cleft palate and hydronephorosis), and functional toxicity, including modulation of immune response. Long-term effects of exposure are of interest, especially as exposure may impact humans. Animal studies have shown relatively long-term immunosuppression following perinatal exposure and increased incidence of soft-tissue neoplastic disease. Despite the abundance of data from animal studies, a great need remains for studies of the effects of TCDD exposure in humans.

Regarding the carcinogenicity of TCDD, several epidemiological studies have found a significant positive association between exposure to dioxin-contaminated phenoxy acids and/or chlorophenols and soft-tissue sarcomas and non-Hodgkins lymphomas. Additionally, in several small industrial cohorts exposed to TCDD-contaminated chemicals, several cases of soft-tissue sarcoma have appeared where none were expected because of the relative rarity of the disease. Also, chloracne was either suspected or confirmed. These studies have several limitations that preclude the estabishment of a causal relationship with TCDD exposure at this time, although several other studies showing no effects suffer from limitations as well. Epidemiological studies are needed to address the toxic manifestations of TCDD in humans.

The results of immune function studies in humans following TCDD (or related chemicals) exposure are ambiguous. Children exposed in the Seveso accident were shown to have significantly elevated lymphoproliferative responses, but other published studies have reported no effects. Unpublished studies have indicated changes in lymphoproliferative responses (both enhancement and suppression) and shifts in lymphocyte subpopulations. Studies of individuals exposed to PCBs have shown that PCBs are immunomodulators in humans, causing suppression of delayed hypersensitivity reactions, enhancement of lymphoproliferative responses, and

increased incidence of infectious diseases. It is not known if these end points can occur in humans exposed to TCDD.

### 3.7.2 Research Needs

Following is a list of research needs related to human health:

- Methods need to be developed to identify persons who have been exposed to TCDD and related chemicals, and to identify more precisely the actual compounds to which they were exposed. This will enable researchers to evaluate more fully the human health effects of exposure.

- Because of the potential for interaction of the halogenated cyclic hydrocarbons (additive, syngeristic, or antagonistic effects), studies are needed to investigate the effects of multiple compounds. This includes identifying human populations exposed to a mixture of compounds, describing the effects of exposure in these populations, and performing laboratory studies on the interaction of compounds.

- When possible, studies should be performed using in vitro exposure of human tissues to dioxins (i.e., human tissues in culture) and the results of these studies utilized to evaluate the studies of in vivo exposure of animals and to facilitate extrapolation to humans.

- Additional epidemiological studies should be accomplished with cohorts not exposed to TCDD or similar chemicals, to establish the baseline for humans for the anticipated end points of toxicity. Although data from animal studies are available in this area, data for human exposure are needed.

- Based on the sensitivity of the immune system (animal studies) to chemical exposure and based on preliminary findings in human populations exposed to TCDD about the importance of the immune system in resistance to neoplastic and infectious disease, additional studies are needed to describe more fully the effects of TCDD and related chemicals on the immune function in humans. Establishing the proper measure of immune function may enable an indication of low-level exposure in humans.

## 3.8 Need For Supply Of TCDD

To date, the toxicity of halogenated dioxins has been determined with studies using only the single compound, TCDD. To evaluate and understand the problems with the complex environmental matrices containing many halogenated dioxins and furans, mixtures of dioxins with and without furans should be studied. This, in turn, requires sufficient quantities of these compounds for toxicology studies.

EPA maintains a repository of purified, analytical-grade pesticides and industrial chemicals for use by scientists throughout the world. This is a very successful program supplying small quantities of standards for chemical assays. In general, commercial chemical companies do not make dioxins and furans available to

toxicologists because of a limited market. Supplies of these chemicals are needed in sufficient quantities and purities for use by toxicologists.

By expanding current and proposed studies to include other dioxins and furans with the study of TCDD, data will be generated that will be significantly more useful to EPA by better focusing on the problems in dump sites and other areas of interest. If the compounds are not available for a few years, answers to the critical questions about dump sites could be delayed a decade or more because many of the studies would have to be repeated to incorporate the other dioxins and furans. Thus, we recommend that the EPA support production and supply these compounds to investigators studying dioxins and furans.

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# CHAPTER 4

# SUMMARY

In order to understand the effects of transport and fate of dioxins and related isomers through environmental media and, ultimately, bioavailability to humans, there are four areas of research needing critical attention: physical and chemical data, field studies, modelling, and human effects studies. Implicit in all of these is a need for adequate supplies of and laboratory standards for all possible isomers and compounds of dioxins and furans, to ensure quality assurance and quality control.

## 4.1 Physical and Chemical Data

The physical and chemical properties of TCDD isomers, other dioxins, and furans need to be further investigated in order to analyze their behavior within environmental media. This workshop has recommended the use of the structure-activity relationship approach, based on thermodynamic consideration. An increased data base will further enhance estimations of partitioning behavior across abiotic interfaces, which will aid estimates of bulk transport and intermedia transfer processes. Understanding intermedia transfer processes can aid in the investigations of methodologies for degrading dioxins in the environment, through photolysis, chemical transformations, or biological processes, ultimately, expansion of the information on physical and chemical properties of dioxins and related isomers will assist the investigations of ecosystem-level processes affecting and being affected by these chemicals and will add further information to answer questions about bioavailability to humans and effects on human tissues and organs.

## 4.2 Field Studies

In order to supplement and enhance the results of laboratory research on basic questions of physical and chemical behavior of dioxins, output from field studies is needed. Information can be used to verify and validate modelling and laboratory work, as well as provide basic data on observed environmental effects. Particularly for the issue of bioavailability in ecosystems, a full-scale field study needs to be conducted at a highly contaminated site. This should include studies of transport and fate, chronic effects, and ecological processes. Such a field study should be closely linked to laboratory investigations.

## 4.3 Modelling

Further efforts need to be made to develop more accurate and applicable mathematical models to predict exposure concentrations of dioxins in environmental media. Concentrations of dioxins over time in organisms as a function of dose need to

be measured for model development. The food-web conceptual model presented in Chapter 2 can be a base upon which calculations can be made giving initial estimates of dioxin concentrations for components. This generic model can be applicable to both terrestrial and aquatic ecosystems, with more specific detail added as needed. Development of ecosystem-level models should be one major goal of the full-scale field study program.

### 4.5 Summary

Running as a common thread throughout this report is the need for further basic research on the physical and chemical makeup of dioxins and related isomers, compounds, and mixtures. But even more relevant to the end point of all environmental regulations, effects on humans, is a need for a basic understanding of how dioxins relate to the environmental media into which they are released. How they affect and are affected by the physical and chemical processes with which they come in contact as they are transported through the biosphere speaks to the ultimate questions of control and degradation, of exposure, bioavailability, and risk. A focused research plan would seek to understand these most basic processes and interactions, from which base of information adequate assessment can be made of the levels of regulation most practicable.

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