Public Health Risks of the Dioxins

Proceedings of a Symposium held in New York City on October 19-20, 1983 by the Life Sciences and Public Policy Program of The Rockefeller University

William W. Lowrance, *Editor*

Public Health Risks of the Dioxins

Proceedings of a Symposium held in New York City on October 19-20, 1983
by the Life Sciences and Public Policy Program
of The Rockefeller University

William W. Lowrance, *Editor*

Library of Congress Cataloging in Publication Data

Main entry under title:

Public health risks of the dioxins.

Bibliography: p.
Includes index.

1. *Dioxins—Toxicology—Congresses.*
2. *Tetrachlorodibenzodioxin—Toxicology—Congresses.*
3. *Environmentally induced diseases—Congresses.*

I. Lowrance, William W., 1943-
II. Rockefeller University. Life Sciences and Public Policy Program.

RA1242.D55P83 1984 615.9'513 84-17987
ISBN 0-86576-076-4 AACR2

Distributed by William Kaufmann, Inc. 95 First Street, Los Altos, California 94022

Printed in the United States of America

Public Health Risks of the Dioxins

Contents

Preface and Acknowledgments

On October 19-20, 1983, the Life Sciences and Public Policy Program of The Rockefeller University convened a symposium on the Public Health Risks of the Dioxins. This conference was meant to follow upon a previous symposium, held in June 1981, on Assessment of Health Effects at Chemical Disposal Sites.*

Three other institutions served as co-conveners: the Sloan-Kettering Institute of the Memorial Sloan-Kettering Cancer Center (Richard A. Rifkind, Director); the Environmental Sciences Laboratory of the Mt. Sinai School of Medicine (Irving J. Selikoff, Director); and the Division of Environmental Sciences of the Columbia University College of Physicians and Surgeons (I. Bernard Weinstein, Director).

Participants included a wide variety of scientific experts and leaders from industry, government, special-interest groups, academia, and the press (listed at end of this volume). Selection of the 400-some participants was based on advice gathered by iterative polling of the leaders of organizations that have worked on the dioxin problem. William W. Lowrance, Director of the Life Sciences and Public Policy Program, chaired the symposium.

Experts in specialties from analytic chemistry to pathology to biostatistics, approached on short notice, delivered presentations in the meeting. Lively panel and audience discussions followed. After the symposium the authors, joined by colleagues, prepared the papers published here. Thus these articles reflect the discussions during the meeting, and afterthoughts.

This symposium was organized as a meeting of scientists and physicians to discuss the difficult technical issues, not to argue about political, legal, economic, and other nonscientific issues, which need different forums. Good-faith respect for these intentions was observed by the participants during the entire two-day symposium.

As became exhaustingly clear during our fundraising efforts,

three kinds of projects are anathema to most philanthropic foundations: conferences, conferences on controversial subjects, and conferences leading to publications. This project, attempting to meet a pressing public need, was of course all three. And our leadtime was much shorter than foundations usually require. Therefore we are extremely grateful to those who responded to our urgent request for funding:

Charles Stewart Mott Foundation
Merck & Co., Inc.
Rockefeller Family Fund
Syntex Corporation
The New York Times Company Foundation.

Because no honoraria and few travel funds were available, it is a tribute to the dedication of the 400 participants and their institutions that almost all of them paid their own expenses to take part in this conference.

Susan Sheridan administered all the preparations for the symposium. The staff of Automated Text, Inc., stalwartly "processed" the drafts of the manuscripts through many revisions. And Carol Moberg served resourcefully as managing editor to direct the publication of these proceedings.

*Assessment of Health Effects at Chemical Disposal Sites (William Kaufmann, Inc., Los Altos, CA, 1981).

Interpretive Summary of the Symposium

William W. Lowrance

(This summary and commentary on the symposium seeks to describe the background on dioxins, summarize the principal themes of concern and areas of apparent agreement, point out areas of uncertainty and disagreement, list some ongoing activities, and suggest implications for research and policymaking. This is not a consensus document, but an interpretation.)

PURPOSE OF THE SYMPOSIUM

The symposium was convened to: (a) develop critical review of scientific issues surrounding the human health risks from low-level exposure to the dioxins; (b) address scientific questions relevant to impending public policy and managerial decisions, and to the research agenda; (c) examine the dioxins as prototypes of other issues of this kind that will be arising; and (d) offer the newsmedia an opportunity to summarize and interpret these issues for the public.

The symposium did not discuss details of the origins of the dioxins or approaches to environmental decontamination, but focussed on biological and health issues.

The goal was to encapsulate, critique, and discuss current understanding, draw out lessons for other such hazard situations, and make suggestions for action.

OVERVIEW OF THE DIOXINS PROBLEM

The dioxins are a family of 75 closely related compounds that occur as trace environmental contaminants. They constitute a major public concern and toxicological puzzle. Their risks to humans still are not well understood or precisely estimated.

Occurrence of the dioxins. The dioxins have never been manufactured deliberately, although small amounts have been synthesized in laboratories for experimental use. In some situations these compounds have been generated as inadvertent and unwanted by-products in manufacture of chemicals based on chlorinated phenols. In some cases, such as in phenolic wood-preservation uses, and in areas sprayed with the herbicide "2,4,5-T" [(2,4,5-trichlorophenoxy)acetic acid, containing residual dioxin contaminants] for civilian forestry or weed-control or military defoliant programs, the dioxins are dispersed and are slowly decaying. In other cases, such as at industrial sites where these materials have been handled, small concentrated pockets of the toxins exist. In a few cases, such as at the former hexachlorophene plant at Seveso, Italy, or on roadways and farms in Missouri, the materials have been released by unusual circumstances -- at Seveso by explosion of the plant, at Times Beach by spraying of waste oil (containing dioxins) for dust control.

There have been some occupational exposures, in manufacturing, in formulation and spraying, and in cleanup of spills and other releases. Fires involving heavy electrical equipment can release dioxins, that either exist in polychlorinated biphenyl (PCB) electrical insulating fluid, or are formed from the PCBs or contaminating chlorobenzenes by oxidation in the fire. Also, it is becoming clear that under some circumstances when hydrocarbons are incinerated in the presence of chlorine radicals, traces of dioxins can be produced in the flames; the extent to which this can contribute to the environmental dioxin burden is now being investigated. Different geneses produce different mixtures of the 75 dioxin compounds.

Search and cleanup. At present, extensive tests are being conducted in a number of countries to analyze for dioxins in air, soils, waters, fish, foods, and animal and human tissues.

Because of health concern, extreme precautions now are being taken to prevent formation and release of dioxins in most situations where they could possibly be generated. Where dioxins have been found, cleanups are being undertaken. Research is underway to

devise methods for ultimate destruction of the dioxins collected in cleanups.

Physical properties. The dioxins are extremely stable physically and biologically. In the environment they do decay, but slowly. The dioxins are virtually insoluble in water, but are soluble in organic solvents and fats and oils. (Thus they tend to precipitate to the bottoms of waterways, and to concentrate in the fatty tissues of fish, animals, and humans.) Dioxins adsorb onto soil particles and are not easily desorbed. They do not burn readily.

TCDD. For several decades research has focussed primarily on 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which on most tests appears to be the most toxic dioxin. A principal issue for current research, now that many other isomers besides TCDD are being studied, is to sort out the extent to which TCDD should be considered the bellwether isomer with respect to health effects.

The furan and PCB connections. A flanking issue should be recognized at the outset: several other sets of compounds that closely resemble the dioxins need to be kept in mind. The dibenzofurans (135 compounds), which are structurally similar to the dioxins, are generated as by-products of some minor manufacturing processes, can be released in electrical equipment fires, and occasionally are encountered from other sources. Besides, many samples of PCBs, upon sensitive analysis, are turning out to contain traces of the dibenzofurans; there is serious speculation that these furans may account for much of the toxicity of PCB fluids. A few other related classes of compounds (chlorinated azoxybenzenes, chlorinated naphthalenes, etc.) also are used in research and commerce.

It was the sense of the symposium that because these compounds appear to be at least as toxic to animals as the dioxins, and occur in much the same kinds of situations, they need to be studied along with the dioxins.

Reasons for health concern. Without question, the dioxins are extraordinarily toxic to rodents and other lower animal species, as

is clear from many of the papers in this symposium. The effects are very dose-dependent.

However, despite passionate concern on the part of many possibly exposed individuals, and despite extensive scientific investigation, it is not obvious that the compounds are so toxic to humans. From several human occupational and accidental incidents, it is evident that at fairly high levels, dioxin exposure causes chloracne (a severe, persistent skin rash) and a variety of other toxic responses. Although chloracne is a reliable sentinel of exposure, absence of chloracne cannot be taken as proof that exposure has not been incurred. Epidemiologic follow-ups have not yet convincingly revealed any increased or unusual pattern of mortality from human exposure. Several symposium papers pursue the controversy surrounding this issue. (The symposium was not able to marshal and review all the direct evidence on humans. Some has been published recently, as cited at the end of this summary.)

Thus the dioxins pose a classic public health dilemma: they are extremely toxic to test animals, but are not clearly so toxic to humans. Human experience is accumulating only slowly. Moreover, most of the human exposures appear to have been very small, and have been incurred under circumstances, such as accidents, sporadic spraying, and war conditions, that make scientific analysis of the exposures and effects very difficult.

THEMATIC ORGANIZATION OF THE SYMPOSIUM

The symposium discussion proceeded from analytic-chemical issues, to human tissue analyses, to small mammal toxicity, to carcinogenicity in rodents, and then to the issue of the principal conjectured human cancer (soft tissue sarcoma), and on through immunotoxicity, reproductive toxicity, and broad metabolic alterations. Then came overviews of actions currently being taken by federal agencies. This was followed by panel discussions of research strategy and agenda. These proceedings are organized in the same way, except that the panel and audience discussions have been woven into the papers or this summary. This overview can only serve to indicate the rich detail carried in the papers themselves.

THE SYMPOSIUM PRESENTATIONS

Overview of biological effects of TCDD in experimental animals. Robert Neal reviewed the great range of effects dioxin has been found to induce in experimental animals. These effects include, variously, induction of the P-450 enzyme system and related enzymes, lethality, a wasting syndrome, hepatic damage, reproductive and teratogenic effects, carcinogenicity, and other toxicities.

The acute lethality of TCDD poses a puzzle, in that the median lethal dose (LD_{50}) differs widely among rodent species: at the extremes, the LD_{50} for the guinea pig is 2 ug/kg, and that for the hamster is over 3,000 ug/kg. Even different strains of mice vary among themselves in susceptibility.

One biochemical mechanism of effect is widely confirmed, and that is the induction of enzymes mediated by a cell-surface receptor (the Ah-locus receptor). But while this accounts for many effects, it may not necessarily account for all the kinds and intensities of effects seen in different experiments. Other mechanisms also are being postulated [see, for instance, the paper by Matsumura et al. in this symposium].

In the animal studies it is not yet settled to what extent biological effects are caused by metabolites of TCDD as opposed to TCDD itself. Dr. Neal concluded that "the acute toxic effects of TCDD appear not to be related, at least directly, to the rate of metabolism in experimental animals nor to the half-life of excretion."

Analytic chemistry and human fat analyses. Analyses have been conducted on blood, milk, and other human fluids and tissues, but usually this has pressed the techniques to the very limits of detection. Dioxins concentrate preferentially in fat tissues and are most readily detected in that material.

Thomas Tiernan described the current capabilities and limitations of methods for analyzing the dioxins and dibenzofurans. Then he reported some observations of dioxins and furans in human tissues from a variety of sources.

Alvin Young and Christoffer Rappe reported analyses of human adipose tissue conducted in their laboratories and elsewhere. As in the Tiernan laboratory, dioxins (and in many cases furans) were reliably detected, isomer-specifically, at levels on the order of 1-10 parts per trillion (ppt). The compounds have been detected in the inhabitants of Seveso, residents of the Canadian and American Great Lakes area, inhabitants of forested areas of Sweden and Canada, Vietnamese and American veterans of the Vietnam War, and firemen and others exposed to the soot and debris from several building fires.

A major drawback is that for most of the tissue analyses reported so far, it has not been possible to know with any certainty the initial exposure experienced by those people.

In view of the slowness and expense of chemical analyses of environmental samples, suggestions were made that inexpensive rapid bioassays be developed for screening.

Many symposium participants now make the working assumption that most members of the general human population carry extremely low background levels of the dioxins and furans (on the order of 1-10 ppt in adipose tissue). Perry Gehring suggested an approach to thinking about this, which he drafted into a brief "think-piece" [included here] after the symposium.

Carcinogenicity. Richard Kociba described his experimental rodent assessment of TCDD carcinogenicity, and the results of other such assays. In a standard experiment, he found that TCDD at 0.07-0.1 ug/kg/day in diet definitely elicited carcinogenic response, in two strains of rats.

Experiments by Alan Poland and others have shown that TCDD acts as a carcinogenic promoter in a special mouse assay in some strains [the Kociba paper summarizes]. Kociba and others have conjectured that, so far, all data suggest that the dioxins' carcinogenesis proceeds through a non-genetic mechanism.

John DiGiovanni [this symposium] reported on a set of

complicating (and possibly opposing) effects, in which the dioxins and other halogenated compounds induce enzyme production that leads to protective, "anticarcinogenic" action. He concluded: "It may, therefore, be very difficult to determine the outcome of exposure to these agents when exposure to other carcinogenic agents occurs at about the same time."

The Kociba tests have been reviewed extensively and have widely been accepted as definitive. The participants in this symposium did not undermine that acceptance, although they raised questions about details. Robert Squire (Johns Hopkins University) has reviewed the pathological analysis from the Kociba experiment. Christopher Portier et al. [this symposium] have conducted an elaborate statistical analysis, based on the Kociba results, to make an estimate of the cancer risk from TCDD exposure. These data have been adopted by the U.S. Centers for Disease Control in establishing a "level for public health concern" [Kimbrough et al., this symposium].

John Van Ryzin reported on the risk projections he, Christopher Portier, and David Hoel have calculated (see Portier et al. paper for mathematical detail). They concluded: "Using linear modelling, the estimated doses which would yield an added risk of one-in-one-million ranged from 38 fg/kg bw/day in female rat livers to 3000 fg/kg bw/day in female mouse subcutaneous tissue." The discussion that followed this paper raised many of the perennial issues concerning such animal tests: how to aggregate various tumors for statistical reckoning; which statistical models to apply; and what these calculations can be taken to imply for human risk.

Renate Kimbrough reported on how the U.S. Centers for Disease Control (CDC) used these carcinogenicity projections to establish guidelines for concern about contaminated residential soil. In essence, Kimbrough et al. have developed a cascade of estimates that proceed from soil contamination levels, to possible exposure from contact and inhalation, to human cancer risk (the latter based on the Portier et al. analyses of the Kociba et al. rat assays). Based on their cautiously weighted sequence of estimations, they concluded that "a soil level of 1 ppb TCDD in residential areas is a

reasonable level at which to express concern about health risks."

[Despite strong qualification by the CDC that this "public-health concern level" is a tenuous, extremely conservative estimate meant only as guidance on soil-borne exposures in residential areas of Missouri, in recent months it has been widely adopted by other authorities, without revision, for many other purposes.]

Bernard Weinstein reviewed current speculations on dioxins as carcinogenic promoters, and expressed strong reservations about the advisability, in environmental regulation, of treating "promoters" differently from "initiators", or epigenetic carcinogens differently from those that appear to act genetically. He recommended that until we know more about the biologic mechanisms, we should treat all substances having carcinogenic properties cautiously and similarly -- not treating TCDD, for example, more leniently than known tumor initiators.

The soft tissue sarcoma problem. The principal form of cancer conjectured to have been associated with exposure to dioxins has been soft tissue sarcoma. Human epidemiologic studies are still being performed, and some that have been completed are quite controversial. No one in the symposium suggested other forms of cancer (these would, of course, be picked up in epidemiologic studies such as worker mortality studies).

Steven Hajdu described the complications encountered in identifying soft tissue sarcomas pathologically. This is a very large family of tumors that can affect many different tissues and take a wide variety of morphologic forms. Too, some non-tumorous pathologies may resemble these sarcomas. Dr. Hajdu criticized the possible misclassification of tumors in some published reports that allege connections between sarcomas and dioxin exposure. He also deplored the publication of medical reports that do not include detailed pathologic information but only summary conclusions. For resolution, he urged formation of a national expert committee to review pathological materials in this problematic area.