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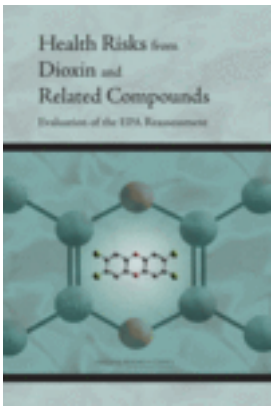

Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment

Committee on EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds, National Research Council

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Although the U.S. Environmental Protection Agency presented a comprehensive review of the scientific literature in its 2003 draft reassessment of the risks of dioxin, the agency did not sufficiently quantify the uncertainties and variabilities associated with the risks, nor did it adequately justify the assumptions used to estimate them, according to this new report from the National Academies&#39 National Research Council. The committee that wrote the report recommended that EPA re-estimate the risks using several different assumptions and better communicate the uncertainties in those estimates. The agency also should explain more clearly how it selects both the data upon which the reassessment is based and the methods used to analyze them.

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Public Summary

HEALTH RISKS FROM TCDD, OTHER DIOXINS, AND DIOXIN-LIKE COMPOUNDS

Evaluation of the EPA Reassessment

Dioxins and dioxin-like compounds (DLCs) are released into the environment from several sources, including combustion, metal processing, and chemical manufacturing and processing. The most toxic of these compounds is TCDD, often simply called dioxin. Many other types of dioxins, other than TCDD, and DLCs share most, if not all, of the toxic characteristics of TCDD. In the past, occupational exposures to TCDD, other dioxins, and DLCs occurred in a variety of industries, especially those involved in the manufacture of trichlorophenol (used to make certain herbicides) and PCBs. (PCBs contain some forms that are dioxin-like and, when heated to high temperatures, may also be contaminated with dibenzofurans, which are also dioxin-like.) Much of the knowledge about the health effects of TCDD, other dioxins, and DLCs in humans comes from studies of relatively highly exposed workplace populations. Widespread use of certain herbicides containing TCDD, other dioxins, and DLCs, as well as some types of industrial emissions, resulted in local and global contamination of air, soil, and water with trace levels of these compounds. These trace levels built up in the food chain because TCDD, other dioxins, and DLCs do not readily degrade. Instead, they persist in the environment and accumulate in the tissues of animals. The general

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public is exposed to TCDD, other dioxins, and DLCs primarily by eating such foods as beef, dairy products, pork, fish, and shellfish.

The health effects of exposures to relatively high levels of dioxin became widely publicized due to the use of the herbicide called Agent Orange in the Vietnam War. Agent Orange contained small amounts of TCDD as a contaminant. Studies suggest that veterans and workers exposed occupationally to TCDD, other dioxins, and DLCs experience an increased risk of developing a potentially disfiguring skin lesion (called chloracne), liver disease, and possibly cancer and diabetes.

Fortunately, background exposures for most people are typically much lower than those seen in either Vietnam veterans or occupationally exposed workers. The potential adverse effects of TCDD, other dioxins, and DLCs from long-term, low-level exposures to the general public are not directly observable and remain controversial. One major controversy is the issue of estimating risks at doses below the range of existing reliable data. Another controversy is the issue of appropriately assessing the toxicity of various mixtures of these compounds in the environment.

In 2004, the U.S. Environmental Protection Agency (EPA), asked the National Research Council (NRC) of the National Academies to review its 2003 draft document titled *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (the Reassessment). This NRC report describes the Reassessment as very comprehensive in its review and analysis of the extensive scientific literature on TCDD, other dioxins, and DLCs. However, the NRC report finds substantial room for improvement in the quantitative approaches used by EPA to characterize risks. In particular, the committee recommends that EPA more thoroughly justify and communicate its approaches to dose-response modeling for health effects and make its criteria for selection of key data sets more transparent. EPA should also improve how it handles and communicates the substantial uncertainty that surrounds its various estimates of health risks from low-level exposures to TCDD, other dioxins, and DLCs. This NRC report provides a critical review of EPA's Reassessment, but the report is not a risk assessment and does not recommend exposure levels for TCDD, other dioxins, or DLCs for regulatory consideration. Rather the NRC report provides guidance to EPA on how the agency could improve the scientific robustness and clarity of the Reassessment for its ultimate use in risk management of TCDD, other dioxins, and DLCs in the environment by federal, state, and local regulatory agencies.

Assessing Human Exposure to TCDD, Other Dioxins, and DLCs

People worldwide are exposed to background levels of TCDD, other dioxins, and DLCs. Background exposures include those from the commer-

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cial food supply, air, water, and soil. EPA's 2003 draft Reassessment does not identify many specific direct sources of human exposures to relatively high levels of TCDD, other dioxins, or DLCs. EPA estimated background concentrations based on studies conducted at various locations in North America. Those studies examined a small number of locations and, hence, may not fully characterize national variability. EPA derived its estimates of TCDD, other dioxins, and DLCs in food from statistically based national surveys, nationwide-sampling networks, food fat concentrations, and environmental samples of air, water, soil, and food.

According to recent estimates, background concentrations of TCDD, other dioxins, and DLCs continue to decline. EPA's estimates of releases of these compounds to air, water, and land from reasonably quantifiable sources in 2000 showed a decrease of 89% from its 1987 estimates. At least one U.S. study determined that meat contains lower levels of TCDD, other dioxins, and DLCs than samples from the 1950s through the 1970s. An ongoing national study by the U.S. Department of Agriculture of the concentrations of TCDD, other dioxins, and DLCs in beef, pork, and poultry should allow for a time-trend analysis of food concentrations.

To assess the total magnitude of emissions of TCDD, other dioxins, and DLCs, EPA used a "bottom-up" approach that attempted to identify all emission-source categories (such as combustion, metal processing, and chemical manufacturing and processing) and then estimated the magnitude of emissions for each category. The committee concludes that a "top-down" approach would also provide useful information and could give rise to significantly different estimates of the historical levels of emissions of TCDD, other dioxins, and DLCs. A top-down approach would account for measured levels in humans and the environment and consider the emission sources required to account for these levels.

The committee also recommends that EPA set up an active database of *typical* concentrations for TCDD, other dioxins, and DLCs present in food. This database should be based on a collection of all available data and updated on a regular basis with new data as they are published in the peer-reviewed literature.

Cancer Risk and TCDD, Other Dioxins, and DLCs

The EPA Reassessment revisits EPA's classification of TCDD, other dioxins, and DLCs on their potential to cause cancer in humans. In 1985, EPA classified TCDD as a "probable human carcinogen" based on the data available and EPA's classification criteria in place at the time. The Reassessment, which revisited this issue given the current evidence and a different draft classification scheme, characterized TCDD as "carcinogenic to humans." In 2005, after completion of the Reassessment, EPA further revised

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its cancer guidelines. In its charge, the NRC committee was specifically asked to address "the scientific evidence for classifying TCDD as a human carcinogen."[1] Referring to the definitions of chemical carcinogens in the EPA's current cancer guidelines, the NRC committee was split on whether the evidence from available studies met *all* the criteria necessary for definitive classification of TCDD as "carcinogenic to humans," although the committee unanimously agreed on a classification for TCDD of at least "likely to be carcinogenic to humans." The committee believed that the *public health* implications of the two terms appeared identical and for this reason did not belabor the issue of classification. The committee concluded that because the definition of "carcinogenic to humans" changed somewhat from previous EPA guidelines and after submission of the Reassessment, EPA should reevaluate its 2003 conclusion based on the criteria set out in its 2005 cancer guidelines.

The committee agrees with EPA in classifying other dioxins and DLCs as "likely to be carcinogenic to humans." However, because mixtures of DLCs and other dioxins may include TCDD, EPA should reconsider its classification of such mixtures as "likely to be carcinogenic to humans" if it continues to classify TCDD as "carcinogenic to humans."

Estimating Cancer Risks at Very Low Doses

Nearly all relevant cancer-risk data from human epidemiological studies and experimental animal bioassays reflect doses much higher than those typically experienced by humans from exposure to TCDD, other dioxins, and DLCs in the general environment. Consequently, analysts must extrapolate well below the doses observed in the studies to consider typical human exposure levels. This extrapolation involves two critical decisions: (1) selecting a "point of departure" (POD), which corresponds to the lowest dose associated with observable adverse effects within the range of data from a study, and (2) selecting the mathematical model used to extrapolate risk from typical human exposures that are well below the POD.

In general, EPA estimates the POD by setting it equal to the dose producing the smallest positive effect observed in a study. The size of the health effect it produces in the population determines the "effective dose." For example, the 1% effective dose (referred to as the ED_{01}) elicits an additional 1% response and the ED_{05} elicits an additional 5% response

[1]The charge to the committee was to evaluate EPA's Reassessment of dioxins and DLCs. Although other agencies, such as the International Agency for Research on Cancer (IARC), have also done both qualitative and quantitative evaluations of dioxin carcinogenicity, the committee focused solely on EPA's Reassessment document, the associated scientific evidence, and EPA's definitions for carcinogen classification.

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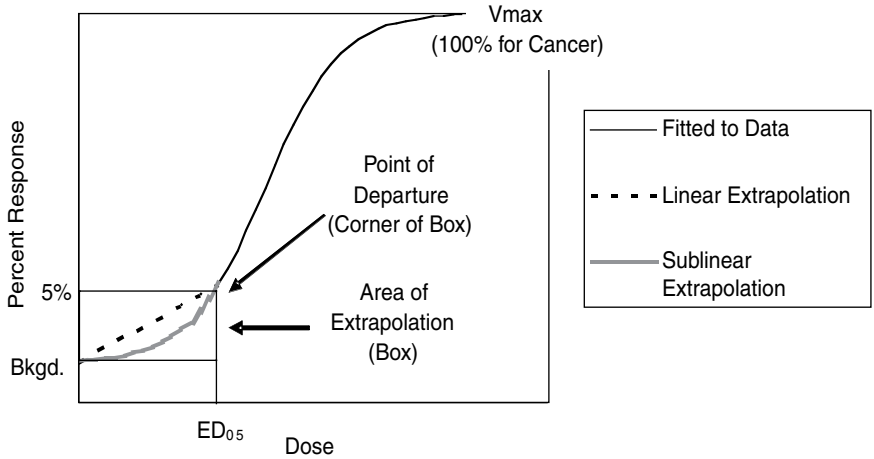

FIGURE S-1 Conceptual illustration of the effect of the selection of the point of departure and the mathematical model used to extrapolate below the point of departure on the risk estimate. Note that the 5% response rate is not drawn to scale. If it were, the area of the extrapolation box would be much smaller. In this illustration, the ED_{05} has been selected as the point of departure for extrapolation to lower doses.

above the "background" response (the level of response that occurs in the absence of any exposure). The response size depends on the difference between the unexposed population and the largest response possible. For example, consider the case of a 25% lifetime background risk of death from cancer in an unexposed population and a highest possible cancer death rate of 100%. In this case, the ED_{01} is the dose that increases the cancer death rate by 1% of the difference between 100% and 25%, or by 0.75%. Thus, the ED_{01} is the dose that increases the risk of dying from cancer from 25% to 25.75%.

Estimating risks below the POD requires making assumptions about how TCDD, other dioxins, and DLCs might cause cancer at lower exposures. For example, in the hypothetical illustration in Figure S-1, a biological mode of action implying that risk is proportional to dose would correspond to use of the dashed line below the POD. A biological mode of action implying a sublinear dose-response relationship would correspond to the shaded line below the POD.

The committee concludes that EPA's decision to rely solely on a default linear model lacked adequate scientific support. The report recommends that EPA provide risk estimates using both nonlinear and linear methods to extrapolate below PODs. If background exposures to humans result in

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doses substantially less than the dose associated with the POD (the most likely case in most instances but perhaps not for occupational exposures), then an estimate of risk for typical human exposures to TCDD, other dioxins, and DLCs would be lower in a sublinear extrapolation model than in the linear model. Given the important regulatory implications of this assumption, the committee recommends that EPA communicate the scientific strengths and weaknesses of both approaches so that the full range of uncertainty generated by modeling of the data is conveyed in the Reassessment.

The committee also concluded that EPA did not adequately quantify the uncertainty associated with responses at the estimated value of the POD. The estimated value of the response at a particular effective dose (like the ED_{01}) is typically uncertain for a variety of reasons related to the challenge of conducting an epidemiological study or an animal study. For example, in epidemiological studies, the number of enrolled subjects is limited, it can be difficult to estimate the actual level of exposure, other factors (such as smoking or exposure to other chemicals) can also cause cancer, and so forth. The committee concludes that, although EPA discussed many of these factors qualitatively, the agency should strive to more comprehensively characterize the impact of these sources of uncertainty quantitatively.

Estimating Noncancer Risk

To characterize the risks of adverse health effects other than cancer, EPA typically identifies a dose, called the reference dose (RfD), below which it anticipates no adverse effects from exposure even among sensitive members of the population. EPA did not estimate an RfD for TCDD, other dioxins, or DLCs in the Reassessment. The committee suggests that estimating an RfD would provide useful guidance to risk managers to help them (1) assess potential health risks in that portion of the population with intakes above the RfD, (2) assess risks to population subgroups, such as those with occupational exposures, and (3) estimate the contributions to risk from the major food sources and other environmental sources of TCDD, other dioxins, and DLCs for those individuals with high intakes.

Given the existing data, the committee concurs with the conclusion in EPA's Reassessment that TCDD, other dioxins, and DLCs are likely to be human immunotoxicants at "some dose level." However, the report finds this conclusion inadequate. The committee recommends that EPA add a section or paragraph to its Reassessment on the immunotoxicology of TCDD, other dioxins, and DLCs in the context of the biological mechanisms responsible for health effects relevant to assessing the likelihood of such effects occurring in humans at relatively low levels of exposure. The

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risk characterization should provide some insight about the level of risk given actual exposures.

Studies show that TCDD, other dioxins, and DLCs cause embryonic and fetal development and reproduction problems in rodents and some other species. However, the fetal rodent clearly shows more susceptibility to adverse effects of TCDD, other dioxins, and DLCs than the adult rodent. Given the lack of comparable human data, the committee recommends that EPA more thoroughly address how animal pregnancy models might relate to human reproductive and developmental toxicity and risk information.

The committee further recommends that, in areas with substantial amounts of human clinical data and epidemiological data, EPA establish formal, evidence-based approaches, including but not limited to those for assessing the quality of the study and study design for classifying and statistically reviewing all available data.

Communicating Variability and Uncertainty in Risk Estimates

Risk assessors must make many choices as they develop models to characterize risks, including selecting appropriate data sets for low-dose extrapolation, dose-response models, PODs, and so forth. Because risk estimates reflect numerous sources of uncertainty and alternative assumptions, EPA's Reassessment should include a detailed discussion of variability (the range of risks reflecting true differences among members of the population due to, for example, genetic and age differences) and uncertainty (the range of plausible risk estimates arising because of limitations in knowledge). Although EPA addressed many sources of variability and uncertainty qualitatively, the committee noted that the Reassessment would be substantially improved if its risk characterization included more quantitative approaches. Failure to characterize variability and uncertainty thoroughly can convey a false sense of precision in the conclusions of the risk assessment.

Estimating Toxicity of DLCs and Mixtures in the Environment

Risk managers base their decisions about cleanup and control of chemicals, such as TCDD, other dioxins, and DLCs, in the environment on assessment of the risks. Because of the common mode of action in producing health effects, EPA's Reassessment assessed the cumulative toxicity of the compounds. The approach taken by EPA and international public health organizations relies on assigning each compound (dioxins, other than TCDD, and DLCs) a "toxic equivalency factor," which is an estimate of the toxicity of the compound relative to TCDD. For example, a particular DLC

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thought to result in one-tenth the risk of TCDD for the same level of exposure would be assigned a toxicity equivalency factor of 0.1.

Because some mixtures may contain little or no measurable TCDD but relatively large amounts of other dioxins and/or DLCs, the toxic equivalency factor plays a critical role in determining the mixture's overall estimated toxicity (which is called the toxic equivalency quotient). Estimation of TEFs is a critically important part of the risk assessment of environmental mixtures of TCDD, other dioxins, and DLCs, because any environmental sample typically contains a dozen or more similar substances, but often very little TCDD. Also, TCDD, other dioxins, and DLCs break down at different rates in the environment and are eliminated at different rates in humans. Thus, although analysts may reasonably estimate the relative potency value for a given compound based on toxicity tests, the compound's contribution to total risk in an environmental (or biological) sample may change over a period of many years. This change may occur because the relative concentration in a sample may change with time, even though the potency remains constant, and the estimated risk in a given sample depends on both potency and concentration.

Even with the inherent uncertainties, the committee concludes that the toxic equivalency factor methodology provides a reasonable, scientifically justifiable, and widely accepted method to estimate the relative potency of DLCs. However, the committee noted that the Reassessment should acknowledge the need for better uncertainty analysis of the toxicity values and should provide at least some initial uncertainty analysis of overall toxicity of environmental samples.

CONCLUDING REMARKS

The committee appreciates the dedication and hard work that went into the creation of the Reassessment and commends EPA for its detailed evaluation of an extremely large volume of scientific literature (particularly Parts I and II of the Reassessment). The NRC report focused its review on Part III of the Reassessment and offers its recommendations with the intention of helping to guide EPA in its efforts to make and implement environmental policies that adequately protect human health and the environment from the potential adverse effects of TCDD, other dioxins, and DLCs. The committee recognizes that it will require a substantial amount of effort for EPA to incorporate all the changes recommended in this NRC report. Nevertheless, the committee encourages EPA to finalize the current Reassessment as quickly, efficiently, and concisely as possible after addressing the major recommendations in this report. The committee notes that new advances in the understanding of TCDD, other dioxins, and DLCs could require reevaluation of key assumptions in the EPA risk assessment docu-

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ment. The committee recommends that EPA routinely monitor new scientific information related to TCDD, other dioxins, and DLCs, with the understanding that future revisions should provide risk assessment based on the current state-of-the-science. However, the committee also recognizes the importance of stability in regulatory policy to the regulated community and thus suggests that EPA establish criteria for identifying when compelling new information warrants science-based revisions in its risk assessment. The committee finds that the recent dose-response data released by the National Toxicology Program after submission of the Reassessment represent good examples of new and compelling information that warrants consideration in a revised risk assessment.

COMMITTEE'S KEY FINDINGS

The committee identified three areas that require substantial improvement in describing the scientific basis for EPA's dioxin risk assessment to support a scientifically robust risk characterization:

- Justification of approaches to *dose-response modeling* for cancer and noncancer end points.
- Transparency and clarity in *selection of key data sets* for analysis.
- Transparency, thoroughness, and clarity in *quantitative uncertainty analysis*.

The following points represent Summary recommendations to address the key concerns:

- EPA should compare cancer risks by using both a linear model and a nonlinear model consistent with a receptor-mediated mechanism of action and by using epidemiological data and the new NTP animal bioassay data. The comparison should include upper and lower bounds, as well as central estimates of risk. EPA should clearly communicate this information as part of its risk characterization.
- EPA should identify the most important data sets to be used for quantitative risk assessment for each of the four key end points (cancer, immunotoxicity, reproductive effects, and developmental effects). EPA should specify inclusion criteria for the studies (animal and human) used for derivation of the benchmark dose (BMD) for different noncancer effects and potentially for the development of RfD values and discuss the strengths and limitations of those key studies; describe and define (quantitatively to the extent possible) the variability and uncertainty for key assumptions used for each key end-point-specific risk assessment (choices of data set, POD, model, and dose metric); incorporate probabilistic models to the

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extent possible to represent the range of plausible values; and assess goodness-of-fit of dose-response models for data sets and provide both upper and lower bounds on central estimates for all statistical estimates. When quantitation is not possible, EPA should clearly state it and explain what would be required to achieve quantitation.

- When selecting a BMD as a POD, EPA should provide justification for selecting a response level (e.g., at the 10%, 5%, or 1% level). The effects of this choice on the final risk assessment values should be illustrated by comparing point estimates and lower bounds derived from selected PODs.
- EPA should continue to use body burden as the preferred dose metric but should also consider physiologically based pharmacokinetic modeling as a means to adjust for differences in body fat composition and for other differences between rodents and humans.

The committee encourages EPA to calculate RfDs as part of its effort to develop appropriate margins of exposure for different end points and risk scenarios.

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Acknowledgment of Review Participants

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by William Halperin and John Bailar. Appointed by the National Research Council, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Preface

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), also called dioxin, is among the most toxic anthropogenic substance ever identified. TCDD and a number of similar polychlorinated dioxins, dibenzofurans, and coplanar polychlorinated biphenyls (dioxin-like compounds [DLCs]) have been the subject of intense scientific research and frequently controversial environmental and health policies. Animal studies have demonstrated potent effects of TCDD, other dioxins, and many DLCs on tumor development, birth defects, reproductive abnormalities, immune dysfunction, dermatological disorders, and a plethora of other adverse effects. Because of their persistence in the environment and their bioaccumulative potential, TCDD, other dioxins, and DLCs are now ubiquitous environmental pollutants and are detected at low concentrations in virtually all organisms at higher trophic levels in the food chain, including humans. Inadvertent exposures of humans through industrial accidents, occupational exposures to commercial compounds (primarily phenoxyacid herbicides), and through dietary pathways have led to a wide range of body burdens of TCDD, other dioxins, and DLCs, and numerous epidemiological studies have attempted to relate exposures to a variety of adverse effects in humans.

Because of substantial policy and economic implications associated with the regulation of TCDD, other dioxins, and DLCs in the environment, the U.S. Environmental Protection Agency (EPA) began in the mid-1980s to invest enormous efforts in risk assessment of these compounds. Many scientists in the dioxin research community participated in writing numerous review chapters on various aspects of dioxin toxicology, chemistry, and environmental fate. In September 1992, initial drafts of all background chap-

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ters of the EPA assessment underwent extensive peer review, followed by extensive revision and additional review of some chapters. In September 1994, all the chapters, plus the first draft of a summary "risk characterization" chapter, were subjected to more peer review and public comment. In 1997 and 1998, additional modifications of the compiled information led to the development of an "Integrated Summary and Risk Characterization" document. This document, as well as additional information on toxic equivalency of DLCs, was revised and subsequently reviewed by EPA's Science Advisory Board (SAB) in November 2000. Recognizing the broad policy implications of the dioxin reassessment, an Interagency Working Group (IWG), consisting of representatives of seven federal agencies, was established in 2000 to foster information sharing, develop a common language for dioxin science and science policy across governmental agencies and programs, identify gaps and needs in dioxin risk assessment, and coordinate risk management strategies. The IWG has provided input to EPA on the draft dioxin reassessment and has been coordinating risk management issues on TCDD and other dioxins for the federal government since its inception. After further revisions in response to SAB and other public comments, in December 2003, EPA released a preliminary draft document titled *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds*, referred to in this report as the Reassessment.

In the summer of 2004, EPA requested the National Research Council (NRC) to create "an expert committee to review EPA's draft reassessment of the risks of dioxin and dioxin-like compounds." In response, the NRC appointed the Committee on EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds, which was charged, to the extent possible, to review "EPA's modeling assumptions, including those associated with dose-response curve and points-of-departure dose ranges and associated likelihood estimates for identified human health outcomes; EPA's quantitative uncertainty analysis; EPA's selection of studies as a basis for its assessments and gaps in scientific knowledge." The charge also requested that the committee address two specific points of controversy: (1) the scientific evidence for classifying dioxin as a human carcinogen, and (2) the validity of the nonthreshold linear dose-response model and the cancer slope factor calculated by EPA through the use of this model. The committee was also asked to comment on the usefulness of toxic equivalency factors (TEFs) and the uncertainties associated with their use in risk assessment of complex mixtures. Finally, the committee was also asked to review the uncertainty associated with the Reassessment's approach to the analysis of food sampling and human dietary intake data.

The entire Reassessment consists of three parts totaling more than 1,800 pages of scientific review. Part I contains several volumes of a previous sci-

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entific review of information relating to sources and exposures to TCDD and other dioxins in the environment, and Part II contains detailed reviews of scientific information on the health effects of TCDD, other dioxins, and DLCs. The information in Parts I and II were provided to the committee as background, with the recognition that many chapters in these two volumes have not been updated for several years. The committee was asked to focus its review on Part III of the Reassessment, which represents an "integrated summary and risk characterization for TCDD and related compounds."

The committee held five meetings between November 22, 2004, and July 7, 2005. The first three meetings provided opportunity for public input. The committee heard from scientists from the IWG, EPA, Food and Drug Administration, Department of Agriculture, Agency for Toxic Substance and Disease Registry, National Center for Health Statistics, and National Toxicology Program and from representatives from academia, environmental organizations, and the regulated community. The committee was provided with written testimony and new scientific papers that have appeared since 2003 (and thus were not available for consideration by EPA in the Reassessment).

It is important to recognize what the committee did not consider to be part of its charge. Although the committee made every effort to consider critical new studies that have appeared since the last revision of Part III of the Reassessment, it did not conduct an exhaustive and detailed review of all scientific information published on TCDD and other dioxins since 2003, and any information that became available to the public after the date of the committee's last meeting (July 7, 2005) was not considered. The committee did not attempt to "redo" the risk assessment—rather, it tried to provide constructive comments in areas in which the scientific approaches or justifications were thought to need improvement, the expectation being that EPA might need to reconsider and revise its approaches and documentation accordingly.

The final recommendations of the committee are offered to EPA with the recognition and appreciation of the enormous amount of time and effort that has been committed to the execution of this Reassessment for nearly 14 years. Although many of the comments are, not surprisingly, critical of certain aspects or approaches taken by EPA, the committee was impressed overall with the tremendous dedication and hard work that has gone into the creation of the Reassessment. The committee hopes the report will be of value in assisting EPA to make final changes to Part III that will allow the timely release of a scientifically defensible document. The committee further hopes that this review will help to guide all federal agencies in making rational and defensible health and environmental policies that adequately protect human health and the environment from the adverse effects of TCDD, other dioxins, and DLCs in the environment.

The Committee on EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds was aided immensely by a number of in-

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dividuals. The committee, and especially the chair, would like to thank the NRC study director Suzanne van Drunick for her tireless effort and good humor in directing this project under substantial time constraints. We also appreciate the organizational skills of Liza Hamilton for ensuring that our meetings and travel arrangements went smoothly, and other NRC staff, including Bryan Shipley for his technical assistance, Ruth Crossgrove and Cay Butler for their editorial assistance, Mirsada Karalic-Loncarevic for her reference assistance, and Alexandra Stupple for her production assistance. The committee is also grateful to Kulbir Bakshi, senior program officer; James Reisa, director of the Board on Environmental Studies and Toxicology; and Thomas Burke, professor and associate chair, Johns Hopkins University, for their oversight of the study; and to Ann Yaktine, Food and Nutrition Board, Institute of Medicine, for her contribution. I would like to thank all the committee members for their hard work and their dedication to ensuring that the report stands up to the basic charge that we "ensure that the risk estimates … are scientifically robust." I, the NRC staff, and the committee are indebted to a number of individuals who presented background information, both orally and in writing, that made the committee's understanding of the issues more complete. Thanks especially to Richard Canady, IWG on dioxin, for his assistance in helping to locate speakers and important background documents and to William Farland for his outstanding assistance.

David L. Eaton, *Chair*
Committee on EPA's Exposure and Human Health
Reassessment of TCDD and Related Compounds

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Abbreviations

2-AAF: 2-acetylaminofluorene
AHF: altered hepatocelluar foci
AHR: aromatic hydrocarbon receptor
Ahr$^{-/-}$: AHR null
AIC: Akaike's information criterion
Anti-SRBC: anti-sheep red blood cell
ARNT: AHR nuclear translocator protein
ATSDR: Agency for Toxic Substances and Disease Registry
AUC: area under the curve
BMD: benchmark dose
BMDL: benchmark dose low
BMR: benchmark response
CB: chlorobiphenyl
CI: confidence intervals
CL: volume of blood cleared per unit time
CLB: cumulative lipid burden
COX: cyclooxygenase
COX-2: cyclooxygenase-2
CSF: cancer slope factor
CYP1A: cytochrome P450A1 protein
CYP1A1: cytochrome P4501A1 protein
CYP1A2: cytochrome P4501A2 protein
CYP1B1: cytochrome P4501B1 protein
DHHS: U.S. Department of Health and Human Services
DIM: diindolymethane

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DLCs: dioxin-like compounds
DOD: U.S Department of Defense
DF: dioxins and furons
DFP: dioxins, furons, and PCBs
ED: effective dose
EGFR: epidermal growth factor receptor
EPA: U.S. Environmental Protection Agency
ER: estrogen receptor
FAO: Food and Agriculture Organization of the United Nations
FDA: U.S. Food and Drug Administration
FSH: follicle-stimulating hormone
GGT: γ-glutamyl transpeptidase
GnRH: gonadotropin-releasing hormone
HAH: halogenated aromatic hydrocarbon
hCG: human chorionic gonadotropin
HpCDD: heptachlorodibenzo-*p*-dioxin
HepCB: heptachlorobiphenyl
HxCDD: hexachlorodibenzo-*p*-dioxin
HxCDF: hexachlorodibenzofuran
I3C: indole-3-carbinol
IARC: International Agency for Research on Cancer
ICZ: indolo-[3,2b]-carbazole
IOM: Institute of Medicine
IPCS: International Program of Chemical Safety
IWG: Interagency Working Group
JECFA: Joint Expert Committee on Food Additives
LABB: lifetime average body burden
LD: lethal dose
LED: lowest effective dose
LH: lutenizing hormone
LOAEL: lowest-observed-adverse-effect level
LOD: limit of detection
6-MCDF: 6-methyl-1,3,8-trichlorodibenzofuran
MOE: margin of exposure
mRNA: messenger ribonucleic acid
NAS: National Academy of Sciences
NCEA: National Center for Environmental Assessment
NIEHS: National Institute of Environmental Health Sciences
NIH: National Institutes of Health
NIOSH: National Institute for Occupational Safety and Health
NOAEL: no-observed-adverse-effect level
NOEL: no-observed-effect level
NRC: National Research Council

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NTP: National Toxicology Program
OCDF: octachlorodibenzofuran
OCDD: octachlorodibenzo-*p*-dioxin
PA: plasminogen activator
PAH: polycyclic aromatic hydrocarbon
PAI-1: plasminogen activator inhibitor-1
PBDD: polybrominated dibenzo-*p*-dioxin
PBDF: polybrominated dibenzofuran
PBPK: physiologically based pharmacokinetics
PCB: polychlorinated biphenyl
PCDD: polychlorinated dibenzo-*p*-dioxin
PCDF: polychlorinated dibenzofuran
PeCB: pentachlorobiphenyl
PeCDD: pentachlorodibenzo-*p*-dioxin
PeCDF: pentachlorodibenzofuran
PK: pharmacokinetics
POD: point of departure
PPAR: peroxisome proliferator activated receptor
ppt: parts per trillion
PR: progesterone receptor
QF: quality of fit
REP: relative potency
RfD: reference dose
RR: rate ratio
SAB: Science Advisory Board
SCF: Scientific Committee on Food
SD: standard deviation
SE: standard error
SMR: standardized mortality (morbidity) ratio
T3: triiodothyronine
T4: thyroxine
TCB: 2,2′,5,5′-tetrachlorobiphenyl
TCDD: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TCDF: 2,3,7,8-tetrachlorodibenzo furon
TEF: toxic equivalency factor
TEQ: toxic equivalent quotient
tPA: tissue plasminogen activator
2,4,5-T: 2,4,5-trichlorophenoxyacetic acid
TSH: thyroid-stimulating hormone
UED: upper effective dose
USDA: U.S. Department of Agriculture
WHO: World Health Organization

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