# USEPA's Reassessment of Potential Exposure and Health Risks of Dioxin and Related Compounds

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## Introduction

Scientists from the U. S. Environmental Protection Agency, (USEPA), other Federal agencies and the general scientific community have been involved in a comprehensive, scientific reassessment of dioxin and related compounds since 1991. External review drafts of the reassessment documents entitled "Estimating Exposure to Dioxin and Related Compounds" and "Health Assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds" were made available in September, 1994 by the Agency for public comment and review by the EPA's Science Advisory Board (SAB). This process has been a model for open, participatory environmental health assessment. Extensive comments have been received and will be the basis for revisions to the draft documents. These documents and subsequent comments highlight a number of issues which are of broad scientific interest.

## U.S. Exposure Survey

The Exposure Document provides the first comprehensive survey of U.S. sources of dioxin and related compounds. A large variety of sources of dioxin have been identified and others may exist. The available information suggests that the presence of dioxin-like compounds in the environment has occurred primarily as a result of industrial practices and is likely to reflect changes in release over time. The principal identified sources of environmental release may be grouped into four major types: combustion and incineration sources; chemical manufacturing/processing sources; industrial/municipal processes; and reservoir sources. Although the current draft suggests that municipal and hospital waste incineration may account for the vast majority of known releases, comments suggest the need to reduce these estimates based on changes in numbers of active facilities and technologies applied to incineration. Also, additional sources have been identified and will be further addressed in future versions of the document.

Because dioxin-like chemicals are persistent and accumulate in biological tissues, particularly in animals, the major route of human exposure is through ingestion of foods containing minute quantities of dioxin-like compounds. This results in wide-spread, low-level exposure of the general population to dioxin-like compounds. Certain segments of the population

may be exposed to additional increments of exposure by being in proximity to point sources or because of dietary practices. The levels of dioxin and related compounds in the environment and in food in the U.S. are based on relatively few samples and must be considered quite uncertain. However, they seem consistent with levels measured in a number of studies in Western Europe and Canada. The consistency of these levels across industrialized countries provides reassurance that the U.S. estimates are reasonable. Collection of additional data to reduce uncertainty in U.S. estimates of dioxin-like compounds in the environment and in food represents an important data need. Data collection is currently underway in a series of studies being carried out by EPA and U.S. Department of Agriculture (USDA) scientists. Recent data on levels of dioxin-like compounds in the fat of beef suggests similar, if not slightly lower, levels compared to previous information. Additional food products are being collected for analysis.

## Air to Food Hypothesis

This assessment adopts the hypothesis that the primary mechanism by which dioxin-like compounds enter the terrestrial food-chain is via atmospheric deposition. Dioxin and related compounds enter the atmosphere directly through air emissions or indirectly, for example, through volatilization from land or water or from re-suspension of particles. Deposition can occur directly onto soil or onto plant surfaces. At present, it is unclear whether atmospheric deposition represents primarily current contributions of dioxin and related compounds from all media reaching the atmosphere or whether it is past emissions of dioxin and related compounds which persist and recycle in the environment. Understanding the relationship between these two scenarios will be particularly important in understanding the relative contributions of individual point sources of these compounds to the food chain and assessing the effectiveness of control strategies focussed on either current or past emissions of dioxins in attempting to reduce the levels in food. Commentors have also highlighted the importance of better understanding atmospheric transformation processes in order to adequately model fate and transport of these compounds from source to receptor (human or ecological).

## Toxicity Equivalents

Throughout the reassessment, concentrations of dioxin and related compounds have been presented as TCDD equivalents (TEQs). TCDD is the best studied of this class of compounds and is the reference compound with regard to determination of toxicity equivalence factors (TEFs). The strengths and weaknesses as well as the uncertainties associated with the TEF/TEQ approach have been discussed in detail in the documents but further attention will be needed to provide appripriate perspective on their use. In particular, additional care will be given to delineating the contribution of TCDD, the best studied of these compounds, to estimated TEQ. Use of the TEFs for dioxin-like PCBs in estimating total TEQ has received extensive comment. As noted, the use of the TEQ approach is fundamental to the evaluation

of this group of compounds and as such represents a key assumption upon which many of the conclusions in this reassessment hinge.

## "Background" Exposure

The term "background" exposure has been used throughout this reassessment to describe exposure of the general population, who are not exposed to readily identifiable point sources of dioxin-like compounds. Data on human tissue levels suggest that body burden levels among industrialized nations are reasonably similar. Average background exposure leads to body burdens in the human population which average 40-60 pg TEQ/g lipid (40-60 ppt) when all dioxins, furans and PCBs are included. High-end estimates of body burden of individuals in the general population (approximately the top 10 % of the general population) without additional identifiable exposures may be 2-3 times higher based on available data. While there are some data to suggest that both environmental and human body burdens are on a downward trend, additional information will be needed to establish a baseline upon which to evaluate future measurements.

In addition to general population exposure, some individuals or groups of individuals may also be exposed to dioxin-like compounds from discrete sources or pathways locally within their environment. Examples of these "special" exposures include: occupational exposures, direct or indirect exposure to local populations from discrete sources, exposure to nursing infants from mother's milk, or exposures to subsistence or recreational fishers. Although daily exposures to these populations may be significantly higher than daily exposures to the general population, simply evaluating these exposures as average daily intakes pro-rated over a lifetime might obscure the potential significance of elevated exposures for these sub-populations, particularly if exposures occur for a short period of time during critical times during development and/or growth. This has raised the issue as to the most appropriate „dose metric" to use for dioxin exposure. Exposure levels, intake values, and body burdens have all been used in the past for this purpose. While the current document focusses on body burden, it recognizes that other metrics of exposure may be more appropriate for assessing certain biological responses.

## Mode of Action

This reassessment concludes that the scientific community has identified and described a series of events attributable to exposure to dioxin-like compounds including biochemical, cellular and tissue-level changes in normal biological processes. Binding of dioxin-like compounds to a cellular protein called the "Ah receptor" represents the first step in a series of common biological steps and may be necessary for most if not all of the observed effects of dioxin and related compounds in vertebrates including humans. While binding to the Ah receptor appears to be necessary for all well-studied effects of dioxin, it is not sufficient, in

and of itself, to elicit these responses. Many effects elicited by exposure to 2,3,7,8-TCDD are shared by other chemicals which have a similar structure and Ah receptor binding characteristics. Consequently, the biological system appears to respond to the cumulative exposure of Ah receptor-mediated chemicals rather than to the exposure to any single dioxin-like compound. Based on our understanding of dioxin mechanism(s) to date, it is accurate to say that interaction with the Ah receptor is necessary, that the Ah receptor in humans is similar in structure and binding characteristics to those found in dioxin responsive animals, and that there is likely to be a variation between and within species and between tissues in individual species based on differential responses "down stream" from receptor binding. Initial simplistic attempts to describe dioxin's mode of action as a transcriptional regulator fail to account for recent data that suggests that receptor binding may alter levels of cellular phosphorylation and hormone and growth factor receptor function without impacting transcription. Further work will be needed to understand this complex of inter-related activities.

The reassessment also finds that there is adequate evidence based on all available information, including studies in human populations as well as in laboratory animals and from ancillary experimental data, to support the inference that humans are likely to respond with a broad spectrum of effects from exposure to dioxin and related compounds, if exposures are high enough. These effects will likely range from adaptive changes at or near background levels of exposure to adverse effects with increasing severity as exposure increases above background levels. Enzyme induction, changes in hormone levels and indicators of altered cellular function represent examples of effects of unknown clinical significance and which may or may not be early indicators of toxic response. Induction of activating/metabolizing enzymes at or near background levels, for instance, may be adaptive or may be considered adverse since induction may lead to more rapid metabolism and elimination of potentially toxic compounds, or may lead to increases in reactive intermediates and may potentiate toxic effects. Demonstration of examples of both of these situations is available in the published literature. Clearly adverse effects including, perhaps, cancer may not be detectable until exposures exceed background by one or two orders of magnitude (10 or 100 times). The mechanistic relationships of biochemical and cellular changes seen at very low levels of exposure to production of adverse effects detectable at higher levels remains uncertain and controversial.

## Species Sensitivity

It is well known that individual species vary in their sensitivity to any particular dioxin effect. Human data provide direct or indirect support for evaluation of likely effect levels for several of the endpoints based primarily on animal information although the influence of variability among humans remains difficult to assess. Biochemical, cellular, and organ-level endpoints have been shown to be affected by TCDD, but specific data on these endpoints do not generally exist for other congeners. Despite this lack of congener specific data, there is reason to infer that these effects may occur for all dioxin-like compounds, based on the concept of toxicity equivalence.

Some of the effects of dioxin and related compounds such as enzyme induction, changes in hormone levels and indicators of altered cellular function have been observed in laboratory animals and humans at or near body burden levels of people in the general population. Other effects are detectable only in highly exposed populations, and there may or may not be a likelihood of response in individuals experiencing lower levels of exposure. Adverse effects associated with temporary increases in dioxin blood levels based on short term high level exposures, such as those that might occur in animal experiments, an industrial accident or in infrequent contact with highly contaminated environmental media, may be dependent on exposure coinciding with a window of sensitivity of biological processes.

## Non-Cancer Health Effects

In TCDD-exposed men, subtle changes in biochemistry and physiology such as enzyme induction, altered levels of circulating reproductive hormones, or reduced glucose tolerance, have been detected in a limited number of the few available studies. These findings, coupled with knowledge derived from animal experiments, suggest the potential for adverse impacts on human metabolism, and developmental and/or reproductive biology, and, perhaps, other effects in the range of current human exposures. Given the assumption that TEQ intake values represent a valid comparison with TCDD exposure, some of these adverse impacts may be occurring at or within one order of magnitude of average background TEQ intake or body burden levels. It seems reasonable to infer that, as body burdens increase within and above this range, the probability and severity as well as the spectrum of human non-cancer effects most likely increases. It is not currently possible to state exactly how or at what levels humans in the population will respond but the margin of exposure (MOE) between background levels and levels where effects are detectable in humans in terms of TEQs is considerable smaller than previously estimated. These facts and assumptions lead to the inference that some more highly exposed members of the general population or more highly exposed, special populations may be at risk for a number of adverse effects including developmental toxicity based on the inherent sensitivity of the developing organism to changes in cellular biochemistry and/or physiology, reduced reproductive capacity in males based on change in hormone levels and, perhaps, decreased sperm counts, higher probability of experiencing endometriosis in women, reduced ability to withstand an immunological challenge and others. This inference that more highly exposed members of the population may be at risk for various non-cancer effects is supported by observations in animals, by scientific inference, and by some human information from highly exposed cohorts.

The deduction that humans are likely to respond with non-cancer effects from exposure to dioxin-like compounds is based on the fundamental level at which these compounds impact cellular regulation and the broad range of species which have proven to respond with adverse effects. Since, for example, developmental toxicity following exposure to TCDD-like congeners occurs in fish, birds, and mammals, it is likely to occur at some level in humans. It is not currently possible to state exactly how or at what levels people will respond with adverse impacts on development or reproductive function. Fortunately, there have been few

human cohorts identified with TCDD exposures in the high end of the exposure range, and when these cohorts have been examined, few clinically significant effects were detected. The lack of adequate human information and the focus of most currently available epidemiologic studies on occupationally, TCDD-exposed adult males makes evaluation of the inference, that non-cancer effects associated with exposure to dioxin-like compounds may be occurring, difficult. It is important to note, however, that when exposures to very high levels of dioxin-like compounds have been studied, such as in the Yusho and Yu-Cheng cohorts, a spectrum of adverse effects have been detected in men, women and children. Some have argued that to deduce - that a spectrum of non-cancer effects will occur in humans in the absence of better human data - overstates the science; most scientists involved in the reassessment as authors and reviewers have indicated that such inference is reasonable given the weight-of-the-evidence from available data. As presented, this logical conclusion represents a testable hypothesis which may be evaluated by further data collection.

## Development of Margins of Exposure (MOE)

The likelihood that non-cancer effects may be occurring in the human population at environmental exposure levels is often evaluated using a "margin of exposure" (MOE) approach. A MOE is calculated by dividing the human-equivalent animal LOAEL or no observed adverse effect level (NOAEL) with the human exposure level. MOEs in range of 100-1000 are generally considered adequate to rule out the likelihood of significant non-cancer effects occurring in humans based on sensitive animal responses. The average levels of intake of dioxin-like compounds in terms of TEQs in humans described above would result in body burdens well within a factor of 100 of levels representing lowest observed adverse effect levels (LOAELs) in laboratory animals exposed to TCDD or TCDD equivalents. Our analysis of body burdens in animals and humans relative to effect levels for a number of biochemical, cellular and clearly adverse endpoints has recently been accepted for publication (DeVito, et al., 1995 in press). For several of the effects noted in animals, a MOE of less than a factor of ten, based on intake levels or body burdens, is likely to exist. Based on these data alone, traditional toxicologic approaches for deriving likely NOAELs for humans and translating them into "safe" or "tolerable" levels for regulatory purposes will need to be re-considered. While it is unlikely that any large segment of the human population is incurring an adverse impact from current body burdens, MOEs are less than we once believed.

## Carcinogenicity of Dioxin-Like Compounds

With regard to carcinogenicity, a weight-of-the-evidence evaluation suggests that dioxin and related compounds (CDDs, CDFs, and dioxin-like PCBs) are likely to present a cancer hazard to humans. Extension of this statement of hazard to this broad range of compounds based on TEFs and in the face of limited data to assess cancer hazard of the individual congeners is a critical issue. The epidemiological data alone are not yet deemed sufficient to characterize the cancer hazard of this class of compounds as being "known". However, combining suggestive evidence of recent epidemiological studies with the unequivocal evidence in animal studies and inferences drawn from mechanistic data supports the characterization of dioxin and related compounds as likely cancer hazards, that is, likely to produce cancer in some humans under some conditions. It is important to distinguish this statement of cancer hazard from the evaluation of cancer risk. The extent of cancer risk will depend on such parameters as route and level of exposure, overall body burden, dose to target tissues, individual sensitivity and hormonal status.

While major uncertainties remain, efforts of this reassessment to bring more data into the evaluation of cancer potency have resulted in a risk specific dose estimate (1 X 10-6 risk or one additional cancer in one million exposed) of approximately 0.01 pg TEQ/kg body weight/day. Estimates of exposure associated with other specific risk values (10-5, 10-4, etc.) can be derived by using a low dose linear model. These risk specific dose estimates represent plausible upper bounds on risk based on the evaluation of animal and human data. These values are similar to previous estimates published by the USEPA in 1985 but based on less data. "True" risks are not likely to exceed these values, may be less, and may even be zero for some members of the population.

The current evidence suggests that both receptor binding and some early biochemical events such as enzyme induction are likely to demonstrate low-dose linearity. The mechanistic relationship of these early events to the complex process of carcinogenesis remains to be established. If these findings imply low-dose linearity in biologically-based cancer models under development, then the probability of cancer risk will be linearly related to exposure to TCDD at low doses. Until the mechanistic relationship between early cellular responses and the parameters in biologically based cancer models is better understood, the shape of the dose-response curve for cancer in the low-dose region can only be inferred with uncertainty. Associations between exposure to dioxin and certain types of cancer have been noted in occupational cohorts with average body burdens of TCDD approximately 2 orders of magnitude (100 times) higher than average TCDD body burdens in the general population. The average body burden in these occupational cohorts level is within 1-2 orders of magnitude (10-100 times) of average background body burdens in the general population in terms of TEQ. Thus, there is no need for large scale low dose extrapolations. Nonetheless, the relationship of apparent increases in cancer mortality in these populations to calculations of general population risk remains uncertain.

TCDD has been clearly shown to increase malignant tumor incidence in laboratory animals. It also appears to decrease the incidence of some hormone-sensitive cancers (uterine, mammary) in laboratory rodents. In addition, a number of studies analyzed in this reassessment demonstrate other biological effects of dioxin related to the process of carcinogenesis. Initial attempts to construct a biologically-based model for certain dioxin effects as a part of this reassessment will need to be continued and expanded to accommodate more of the available biology and to apply to a broader range of potential health effects associated with exposure to dioxin-like compounds.

## Summary

Based on all of the data reviewed in this reassessment and scientific inference, a picture emerges of TCDD and related compounds as potent toxicants in animals with the potential to produce a spectrum of effects in animals and, perhaps, in humans. Some of these effects may be occurring in humans at very low levels and some may be resulting in adverse effects on human health. The potency and fundamental level at which these compounds act on biological systems is analogous to several well studied hormones. Dioxin and related compounds have the ability to alter the pattern of growth and differentiation of a number of cellular targets by initiating a series of biochemical and biological events resulting in the potential for a spectrum of responses in animals and humans. Despite this potential, there is currently no clear indication of increased disease in the general population attributable to dioxin-like compounds. The lack of a clear indication of disease in the general population should not be considered strong evidence for no effect of exposure to dioxin-like compounds. Rather lack of a clear indication of disease may be a result of the inability of our current data and scientific tools to directly detect effects at these levels of human exposure. Several factors suggest a need to further evaluate the impact of these chemicals on humans at or near current background levels. These are: the weight of the evidence on exposure and effects; an apparently low margin of exposure for non-cancer effects; and potential for additivity to background processes related to carcinogenicity. Critical issues relating to dioxin exposure and toxicity requiring additional attention in the reassessment include: sparse data to derive national means for sources/pathways; state of validation of exposure models; trends in environmental/body burden levels; TEFs/TEQs; impact of human data on hazard and risk characterization; significance of enzyme induction and other biochemical effects; and the relative roles of data, scientific inference, and science policy in informing regulatory decisions.