USEPA'S RISK CHARACTERIZATION OF DIOXIN AND RELATED COMPOUNDS

William Farland[1], John Schaum[1], Dwain Winters[2], Matthew Lorber[1], David Cleverly[1], Bruce Rodan[1], Linda Tuxen[1], Michael DeVito[3], and Linda Birnbaum[3]

[1]National Center for Environmental Assessment, ORD, USEPA, Washington, DC, USA 20460
[2]Office of Pollution Prevention and Toxics, USEPA, Washington, DC, USA 20460
[3]National Health and Environmental Effects Research Laboratory, ORD, USEPA, RTP, NC 27711

Introduction

Scientists from the Environmental Protection Agency (EPA), other Federal agencies and the general scientific community have been involved in a comprehensive reassessment of dioxin exposure and human health effects since 1991. The final dioxin reassessment will consist of three parts. *Part 1: Estimating Exposure to Dioxin-Like Compounds* will include four volumes that focus on sources, levels of dioxin-like compounds in environmental media, and human exposures. *Part 2: Human Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* will consist of two volumes that include information on critical human health end points, mode of action, pharmacokinetics, dose-response, and TEFs. *Part 3: Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* will be a stand alone document. In this summary and characterization, key findings pertinent to understanding the potential hazards and risks of dioxins are described and integrated, including a discussion of all important assumptions and uncertainties. A draft version of Part 3, along with a chapter on TEFs and the revised Dose Response Chapter from Part 2 are currently undergoing peer review and public comment.

Discussion

Throughout this reassessment, concentrations of dioxin and related compounds are presented as TCDD equivalents (TEQs). The strengths and weaknesses as well as the uncertainties associated with the TEF/TEQ approach have been discussed in the report and, particularly, in a newly developed chapter (Part 2, Chapter 9). The use of the TEQ approach is widely accepted in the international scientific community as fundamental to the evaluation of this group of compounds that always exist in nature as complex mixtures of congeners. The use of the TEQ approach represents a key assumption upon which many of the conclusions in this characterization hinge.

The exposure document (Part 1) has been revised to reflect comments from the public and the Agency's Science Advisory Board (SAB). It presents a comprehensive emission inventory of dioxin and related compounds for the US. A large variety of sources of dioxin have been identified, and characterized but others may exist. The available information suggests that the presence of dioxin-like compounds in the environment has occurred primarily as a result of formation of unintentional by-products of combustion or industrial practices and reflects changes in release over time. The principal identified sources of environmental release are grouped into five types: Combustion and Incineration Sources; Metals Smelting, Refining and Processing; Chemical Manufacturing/Processing; Reservoir Sources; and Biological and Photochemical Processes. The Exposure Document provides "snapshots" of estimated emissions for the years 1987 and 1995. Because of the nature of the available data and the need to extrapolate to estimate

national emission levels, confidence in these estimates varies. However, EPA's best estimates of releases of dioxin and related compounds (CDDs/CDFs) to air, water and land from reasonably quantifiable sources suggests an estimated 80% decrease between 1987 and 1995, due primarily to reductions in air emissions from municipal and medical waste incinerators. Estimates of current releases from municipal and medical waste incinerators and pulp and paper production indicates over 95% reductions from 1987 estimates. A complete inventory update is expected in 2000-2001.

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 exposure of the general population to dioxin-like compounds. Daily intakes have come down since the 1970's and, as of the mid-90's, adult daily intakes of dioxin and related compounds, including dioxin-like PCBs average 70 pg$TEQ_{DFP}WHO_{98}$/day. 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 estimates of dioxin and related compounds in the environment and contributing to daily intakes in the U.S. reflect collection of additional data since 1995.

The reassessment adopts the hypothesis that the primary mechanism by which dioxin-like compounds enter the food web and human diet is via atmospheric deposition. At present, it is unclear whether deposition represents primarily current contributions of dioxin and related compounds from all media reaching the atmosphere or if it represents 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 assessing the relative contributions of point sources of these compounds to the food web and assessing the effectiveness of control strategies focused on current and past emissions in attempting to reduce dioxin exposures.

The term "background" exposure has been used throughout the 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 US background exposure led to body burdens in the human population in the late 1980's which ranged from 30-80 pg TEQ_{DFP}-WHO_{98}/g lipid (this equates to 30-80 ppt), with a mid-point of approximately 55 pg TEQ_{DFP}-WHO_{98}/g lipid, when all dioxins, furans and dioxin-like PCBs are included. High-end estimates of the body burden of individuals in the general population (approximately the top 1% of the general population) may be greater than 3 times higher, based on evaluation of blood-level data and on consumption of fat as a surrogate for dioxin intake. The average CDD/CDF/PCB tissue level for the general adult U.S. population appears to be declining and the best estimate of current (late 1990s) average body burden levels is 25 ppt (TEQ_{DFP}-WHO_{98}, lipid basis). 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 of local populations to discrete sources, or exposure of nursing infants from mother's milk. Daily exposures to these individuals may be significantly higher than daily exposures to the general population. However, the differences in average body burden are expected to be much less than the differences in daily intake, particularly if these elevated exposures are periodic or for short duration. In addition, the

health benefits of dietary choices must factor into the assessment of overall risk.

Subtle changes in biochemistry and physiology such as enzyme induction, altered cellular function, and other potentially adverse effects have been detected in dioxin-exposed populations in a limited number of available studies. EPA has chosen to use body burden as the appropriate dose metric to compare these effects over time and between species, rather than daily intake, because body burden more closely reflects delivered dose to the tissues for persistent compounds. Given the assumption that TEQ body burdens 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. As body burdens increase within and above this range, the probability of non-cancer effects occurring is also likely to increase, accompanied by the likelihood of a broader spectrum of human non-cancer response. Because of the basic biological level at which dioxin and related compounds act, and due to the potential diversity of "down-stream" responses to a dioxin body burden, it is not currently possible to state exactly how or at what levels individuals in the population will respond. It is clear, however, that as recent data have developed, the margin of exposure (M-O-E) between body burdens associated with background levels of exposure and levels where biological changes are detectable in humans, in terms of body burden TEQs, is considerably smaller than previously estimated. For certain biological changes, including subtle behavioral impacts, a "no effect level" has yet to be established.

These facts and assumptions lead to the inference that, within the range of general population exposure, some individuals may be at risk for adverse effects. These effects may include, for instance, developmental toxicity based on the inherent sensitivity of the developing organism to changes in cellular biochemistry and/or physiology, reproductive impacts, reduced ability to withstand an immunological challenge and others. This inference of potential risk is supported by observations in animals, human information, and other scientific observations. Special populations with exposures above that of general population may be at greater likelihood of risk.

With regard to carcinogenicity, a weight-of-the-evidence evaluation suggests that 2,3,7,8-TCDD should be characterized as a " human carcinogen"and that related compounds (other dioxin-like CDDs and CDFs, and dioxin-like PCBs) should be considered "likely" to present a cancer hazard to humans. The epidemiological data alone are not yet deemed sufficient to characterize TCDD as a "human carcinogen." However, combining consistent, suggestive evidence from epidemiology studies with the unequivocal evidence in animal studies and inferences drawn from mechanistic data supports the characterization of complex mixtures of dioxin and related compounds as "likely" cancer hazards. The confidence in this statement for specific environmental mixtures increases with the level of available congener-specific information.

The current evidence suggests that both receptor binding and many early biochemical events such as enzyme induction are likely to demonstrate linearity at the ED_{01} level. The mechanistic relationship of these early events to the complex process of carcinogenesis remains to be established. Until the mechanistic relationships between early cellular responses and the parameters in biologically based cancer models are better understood, the shape of the dose-response curve for cancer below the range of observation can only be inferred with uncertainty. Associations between exposure to dioxin and certain types of cancer risk have been noted in

occupational cohorts with average body burdens of TCDD approximately 1-3 orders of magnitude (10 to 1,000 times) higher than average TCDD body burdens in the general population. In terms of total TEQ, 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. Thus, there is no need for large scale low dose extrapolations to estimate upper bounds on general population cancer risk or to evaluate the impact of incremental exposures above background. Nonetheless, the relationship of apparent increases in cancer mortality in these populations to calculations of general population risk remains uncertain.

While major uncertainties remain in calculating numerical estimates of cancer risk, the inclusion of additional data in this reassessment has resulted in estimates of cancer potency in the range of $5x10^{-3}$ to $5x10^{-4}$ per pgTEQ/kgBW/day. These slope factors and resulting risk specific dose estimates represent a plausible upper bound on lifetime risk based on the evaluation of human and animal data within the range of observation and at the level of a minimally detectable response (ED_{01}). These values are 3 to 30 times higher than previous estimates (1985, 1994), which were based on less data. Using these slope factors and current intake levels, upper bound (>95%-ile) lifetime risks for the general population are in the range of 10^{-3} (1 in 1,000) to 10^{-2} (1 in 100). "True" risks are not likely to exceed this value, are likely to be less, and may even be zero for some members of the population. 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. This range of upper bound risk for the general population is higher by a factor of 10 from the risk described at background exposure levels based on EPA's earlier (1994) draft of this reassessment (10^{-4}-10^{-3}).

Summary and Conclusions

Based on all of the data reviewed in this reassessment and scientific inference, TCDD and related compounds can be characterized as potent toxicants in animals with the potential to produce a spectrum of effects. Some of these effects may be occurring in humans at general population background levels. 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 cancer and non-cancer 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 from 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 apparent low margin-of-exposure for non-cancer effects; potential for significant risks to some portion of the general population and additivity to background processes related to carcinogenicity in the case of incremental exposures above background.

This abstract does not reflect USEPA policy.