THE UNITED STATES ENVIRONMENTAL PROTECTION AGENCY (U.S. EPA) APPROACH TO EVALUATING DIOXIN HEALTH RISKS: CRITICAL ISSUES

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1. 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. Critical issues relating to dioxin exposure and toxicity and 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. Several of these are discussed below.

2. Toxicity Equivalents

Throughout the USEPA 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 appropriate 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. Based on or knowledge of average body burdens, the ratio of TCDD/Total TEQ including PCBs is approximately one order of magnitude ($\leq$ 10).

3. "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 recent data 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.

4. Mode of Action

The USEPA 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. Many of these events are tissue specific. Binding of dioxin-like compounds to a cellular protein called the "Ah receptor" represents the first step in the series 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 many of the 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, but a comprehensive data base does not exist. 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. While on the one hand this supports the importance of considering multiple chemicals in the dioxin reassessment, it raises the interesting issue of the role of the broad

class of Ah receptor-binding compounds occurring naturally in food.

Based on our understanding of dioxin mechanism(s) to date, interaction with the Ah receptor is generally necessary, the Ah receptor in humans is similar in structure and binding characteristics to those found in dioxin responsive animals, and 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 attempts to describe dioxin's mode of action as a "classic" transcriptional regulator fails 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 detectible at higher levels remains uncertain and controversial.

5. Development of Margins-of-Exposure (M-O-E)

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, M-O-Es are less than we once believed.

6. References

DeVito M.J., L.S. Birnbaum, W.H. Farland, and T.A. Gasiewicz (1995) : Comparisons of Estimated Human Body Burdens of Dioxin-like Chemicals and 2,3,7,8-tetrachlorodibenzo-p-dioxin Body Burdens in Experimentally Exposed Animals. Env. Health Pers. In Press