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# Update: The US EPA's Reassessment of Dioxin and Related Compounds.

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On September 13, 1994, The US EPA released drafts of the dioxin reassessment for external comment and review. These documents, totalling approximately 2000 pages, entailed three volumes "Estimating Exposure to Dioxin-Like Compounds" and three volumes constituting a "Health Assessment of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds." These documents reflected over three years of effort by the Agency to reassess the potential risks from exposure to dioxin and related compounds. The reassessment was prompted by the advances in scientific knowledge occurring since the first health assessment document was published in 1985. These advances included increased understanding of the mechanism(s) of action of dioxin, new information on the non-cancer health effects, and additional publications detailing adverse effects in human populations.

The dioxin reassessment involved a multi-pronged approach, including ecological risk, human health risk, and exposure information, all being folded into a final "risk characterization". An interim report on toxicity of dioxin and related compounds to aquatic organisms was peer-reviewed and published in 1993. This document also included information on fate, transport, and bioaccumulation in the environment. The ecological risk assessment has not yet been concluded, and additional information is still being gathered. Early drafts of the health risk assessment document were written by outside authors from academia, other government agencies, and Europe. The chapters concerned pharmacokinetics, mechanisms of action, general toxicity, immunotoxicity, developmental and reproductive effects, cancer, human data, and dose-response modeling. These were peer-reviewed in September, 1992. The epidemiology chapter underwent major revision and was re-reviewed in September, 1993. The exposure document, which involved additional data as well as actual updates on exposure scenarios was prepared by a team of EPA authors from multiple program offices in conjunction with a contractor. This document was also reviewed by an outside panel in September, 1992.

The entire process has been open, participatory, and inclusive. External authors were involved at multiple stages in the preparation of the documents. Intra and Inter-agency reviews were held prior to the release of the drafts. Public information meeting were held in November, 1991 and April, 1992 to get input into the process. Additional public sessions were held in nine locations across the country at the time of the release of the draft in the fall of 1992, followed by a 120 day

public comment period. Scientific "debates" were held at several national meetings. Extensive oral and written comments have been received by the Agency. It is clear that relevant information on dioxin exposure and effects continues to appear in the scientific literature at a rapid rate.

The exposure portion of the documents identifies combustion and incineration as the major sources of dioxins and related compounds in the United States today. Medical and municipal incinerators are the largest contributors. New emissions also are the result of chemical manufacturing and processing. At this point, only 20-50% of the deposition can be accounted for by known emissions. While some of this could be due to uncertainties in the measurements, it is likely that reservoir sources and environmental recycling are significant contributors.

The major pathway for human exposure appears to be via microcontamination of the diet. Animal products ,especially meat, fish, and dairy, are the major contributors. This is due to the propensity for dioxins to persist and bioaccumulate up the food chain. Dioxins are emitted into the air or water and are taken up by animals. This has resulted in widespread, low-level exposure to the general population. It is possible that certain segments of the population may have higher levels due to dietary practices or proximity to point sources. Such proximity could result in exposure via inhalation of vapors and particulate, as well as dermal contact via contaminated soils.

Exposure to dioxins has been evaluated using the toxic equivalency (TEQ) approach. This approach is fundamental to the evaluation of this group of compounds, including the PCDDs, PCDFs, and dioxin-like PCBs, and represents a key assumption upon which many of the conclusions of the assessment are based. 2,3,7,8-TCDD is the best studied of all of the dioxin-like compounds and is used as the reference compound with regard to TEQ. Relative toxic equivalency factors (TEFs) are assigned based on comparison to TCDD. The TEFs are relative potency factors based on inspection of multiple endpoints and incorporating scientific judgment. They represent order of magnitude estimates of the toxicity of compounds. The approach has been characterized by the Agency, various state and local governments, and by the international scientific community as a useful, if uncertain, interim process which has an empirical basis and is theoretically sound. The determination of TEQ, which is based on the sum of the products of the TEF concentration for each congener, relies upon the concept of additivity of effects of dioxin-like compounds, and has been validated with relatively simple mixtures of PCDDS, PCDFs, and PCBs for multiple endpoints. In addition, studies of complex synthetic mixtures have demonstrated additivity with regards to enzyme induction, teratogenicity, tumor promotion, and lethality. Several studies using environmental samples such as Binghamton soot, Love Canal leachate, and fly ash have also shown additivity. Interactions between dioxins and non-persistent Ah agonist, or persistent, non-dioxin-like compounds remain to be elucidated.

The exposure document estimates that the average lipid-adjusted serum level of 2,3,7,8-TCDD is 3-5 PPT in the general population. Incorporating the PCDDs and PCDFs, the average TEQ is approximately 30 PPT. The total TEQ, based on TEF values for the dioxin-like PCDDs, PCDFs. and PCBs, is estimated to average 40-60 PPT. These measurements,

which are based on a limited number of samples in the US but are compatible with data from Canada, the Netherlands, Germany, and Sweden, are associated with daily exposure of 1-3 pg PCDD/PCDF TEQ/kg/day, or 3-6 pg PCDD/PCDF/PCB TEQ/kg/day. Highly exposed populations, such as subsistence fishermen and nursing infants would have greater daily exposures.

The health effects of TCDD have been studied extensively in multiple animal species. Limited information is available on many of the related compounds. At high doses, dioxins caused wasting and delayed lethality. Lymphoid and gonadal atrophy occur at slightly lower doses as do adverse effects on the liver. Both hyperplastic and metaplastic responses are seen in various tissues. The hallmark of dioxin toxicity in people. chloracne, involves both hyperplasia and altered differentiation. Dioxins cause developmental and reproductive effects in multiple species. They are potent immunosuppressants in several species and has been shown to be carcinogenic in four species, which are all that have been tested. Dioxins causes multiple biochemical effects including altered metabolism due to changes in various enzyme systems, altered homeostasis, due to hormonal perturbations, and changes in proliferation and differentiation associated with altered growth factor systems.

Epidemiological studies have shown changes in glucose tolerance and decreases in hormone levels in occupationally exposed populations. These changes are relatively minor for the individual but do suggest an altered distribution of the population. Recently, changes in neurobehavior and hormone levels have been reported in infants whose mothers are at the high end of dioxin TEQ within the general population. In addition, changes in enzyme induction and liver enzymes have been reported in exposed populations, and immunological alterations have been observed. Many of the effects seen are often considered to be adaptive, but they have the potential for adversity. The human cancer data are compatible with the animal data, demonstrating elevated increases in tumor response. Given the mechanistic plausibility underlying dioxin-induced carcinogenesis in people and in multiple species of animals, dioxin is considered a probable human carcinogen. The absence of definitive studies demonstrating nonlinearity at low doses for certain biochemical responses thought to be associated with toxicity and the additivity to background concentrations support the continued use of a linearized multistage model. Further model development to incorporate additional relevant data for both cancer and non-cancer endpoints is clearly warranted.

The WHO tolerable daily intake has been set at 10 pg TCDD/kg/day, based on a safety factor of 100 with a NOEL of 1 ng/kg/day. Accepting the TEF approach and given that the average daily intake is 3-6 pg TEQ/kg/day, there appears to be little or no margin of exposure for a variety of effects caused by dioxins.
It is important to note approximately 5% of the general population have body burdens 2-3 times the average. Decreased testosterone levels and decreased glucose tolerance have been noted at body burdens within a factor of 10 of those in the general population. Effects in experimental animals have been seen at body burdens overlapping those in the general population. In vitro experiments using human cells and tissues have demonstrated equivalent or even greater sensitivity than using material derived from animals.

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Thus, the reassessment has concluded that there is potential for effects to be occurring in the general population from exposure to dioxins and related compounds. It is important that all the compounds that bind tightly to the Ah receptor be included in this evaluation. While food is the major source of exposure to the general population, all sources and pathways must be considered. While there is no less concern about the carcinogenic properties of dioxins, given the results of this reassessment there is increased concern for the non-cancer effects. Whether these are frankly adverse or just indicators of potential responses in the general population remains to be determined.

Public comments provided new data and constructive comments which will be incorporated in the final reassessment documents. There was concern about the sparse data which exists concerning sources and pathways, especially as regards PCBs, in the exposure document. More discussion needs to be included about the development and use of TEFs and the estimation of body burdens. In addition, the significance of biochemical changes needs to be addressed. The roles of scientific data, scientific inferences and science policy need to be clarified. An external panel convened by EPA's Science Advisory Board met in May, 1995 to review the draft documents. They also made constructive comments which will lead to an improved Agency document which can be used to set policy. Until the documents are finalized, policy continues to based on the 1985 assessment.