HEALTH RISK ASSESSMENT FOR DIOXIN AND RELATED CHEMICALS: THE U.S. EPA APPROACH.

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The US EPA has been engaged in a multi-year effort to reassess the health risks from exposure to dioxin and related compounds. This has been an open and participatory process involving scientists from government, academia, industry, and public interest groups. Several rounds of writing, revision, and peer-review have been held. Final versions of the exposure and health chapters have been prepared based on all of the comment received. In addition, two chapters, those on dose/response modeling and the final risk characterization chapter, are being revised for additional peer review prior to finalization by the Agency. Target for completion of these activities is the late fall of 1996. Until the document is finalized, no change in regulatory policy will be based on its findings.

In the past, the US EPA has regulated dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin) as a carcinogen based on the positive animal data and the compatible epidemiological findings. The linearized multi-stage model was used as EPA's default position, in the absence of data to the contrary. Application of this model to the bioassay results from Kociba[1], focusing on the liver tumors in female Sprague-Dawley rats, resulted in an upper bound estimate of an excess of one in a million cancer risk from exposure to 6 fg/kg/day. In the revised document, the linearized multi-stage model is still used because there is evidence which supports linearity in the low dose region of the experimental range for a number of dioxin-mediated responses. Approaches for extrapolation beyond the range of observation are being explored. The Agency has not regulated dioxin based on its non-cancer effects, believing that the use of the LMS model for carcinogenesis would be protective for non-cancer effects as well. Given that current exposure to total TCDD equivalents is approximately 1-3 pg/kg/day, EPA deemed it inappropriate to establish a RfD which would likely be less than the current average daily intake..

The WHO and several other countries have used a different approach to estimating the risk of dioxin. They have used a TDI approach, also based on the two-year Kociba bioassay. They suggested that 1 ng/kg/day was a NOAEL for carcinogenesis. Applying a 10-fold safety factor for interspecies extrapolation and a 10-fold' "correction" for rat/human pharmacokinetic differences, resulted in a TDI of 10 ng/kg/day. This is 1000 times higher than the EPA "one in a million" risk specific dose of 10 fg/kg/day, yet it is based on the same experimental data set. The WHO also suggested that a TDI would be appropriate based on their estimation of a NOAEL of 1 ng/kg/day based on the Murray[2] multigeneration reproduction study.

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Dioxin is but one member of family of chemicals, the polyhalogenated aromatic hydrocarbons, which have a common mechanism of action via the Ah receptor, a common spectrum of responses, and are structurally related. This has led to the development of a relative potency ranking scheme, the toxic equivalency factor approach, in which the relative potency of each dioxin-like compound is expressed as some fraction of that of TCDD. The sum of the product of each compound's TEF times its mass results in the total toxic equivalence (TEQ) of a mixture. This scheme does not take into account non-additive interactions which may result from non-Ah receptor mediated mechanisms or from interactions with chemicals which are not dioxin-like in their properties.

Current exposure to dioxin and related compounds results in approximately 1-3 PCDD/PCDF TEQ/kg/day, or 2-6 TEQ PCDD/PCDF/PCB TEQ/kg/day. This greatly exceeds the US EPA's RSD, and approaches the WHO TDI value. In addition, recent experimental studies in laboratory animals and new data from human populations may cause a reevaluation of the TDI. Reanalysis of the Murray data suggest that 1 ng/kg/day is not a NOAEL but a LOAEL[3]. Immunological effects have been observed following a single dose of 10 ng/kg[4], and developmental/reproductive effects have been seen following a single dose of 50 ng/kg[5] or 64 ng/kg[6] to the pregnant rat. An intensive study of women and their infants in the Netherlands[7] has observed adverse effects on behavioral, immunological and hormonal parameters in the offspring even within the general population, i.e., those with no known exposure other than background. Pharmacokinetic studies have demonstrated that experimental animals and humans handle dioxins in a similar fashion. Recent studies have demonstrated that the body burden appears to be a better dose metric than daily exposure[8,9]. Taken together, these data suggest that the TDI should be established based on the TEQ approach and may need to be lower than previously thought.

The draft of the US EPA's dioxin reassessment[10] suggests that there is little margin of exposure between TEQ levels and adverse health effects. This would be in good agreement with proposals suggesting a lowering of the TDI.

(This abstract does not necessarily represent U.S.EPA policy.)

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