A PROPOSED REFERENCE DOSE FOR DIOXIN OF 1-10 PG/KG-DAY: A WEIGHT-OF-EVIDENCE EVALUATION OF THE HUMAN STUDIES

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Introduction

The dioxins and related chemicals for which toxicity equivalence factors (TEFs) have been established are perhaps the most studied of all chemicals to which humans are routinely exposed. Interest in these chemicals is due to their high acute toxicity in animals, their carcinogenic potency, the range of effects that have been reported in animal studies, their recalcitrance to degradation, and the ubiquitous exposure of humans. The primary concern of regulatory agencies over the past 25 years has been the cancer hazard to humans, although the data seem to suggest that noncancer effects may occur at lower doses.

As a guidance value, the U.S. Environmental Protection Agency (EPA) calculated an ED_{01} of 10-50 ng total TEQ/kg body weight. EPA did not suggest a reference dose (RfD) because, based on their analysis, it would be below the current background body burden (5 ng total TEQ/kg; 0.5 ng TCDD/kg) and therefore of no practical benefit. In this study, we evaluated the most cited and credible human studies that address the noncancer effects of dioxin to calculate an RfD.

Methods

A literature review and analysis was conducted of various toxicological endpoints. Throughout our evaluation, we used the following criteria to identify those studies appropriate for use in establishing a proposed RfD: 1) The endpoint must be adverse; 2) the data must be replicated across multiple studies; 3) sufficient dose-response data must exist to identify both a no-observed-adverse-effect level (NOAEL) and a lowest-observed-adverse-effect level (LOAEL); 4) data from subchronic or chronic studies are preferred to acute (single-dose) studies; and 5) data must be statistically significant. We found no studies in which all criteria were met.

Results and Discussion

ENDPOINTS WITHOUT STRONG SUPPORT: The data on the following endpoints was neither strong, clear, nor consistent enough to use in calculating an RfD (data not shown): Changes in CYP 1A and GGT activity levels; cardiovascular system toxicity; immune system effects; thyroid function; and sex hormones.

ENDPOINTS WITH MODERATE SUPPORT: A complete understanding of any relation between TCDD and diabetes is hampered by the disparity among endpoints examined within the cohorts. The strongest data are from the Ranch Hand study. A comparison of LOAELs and NOAELs based on risk of diabetes in the Ranch Hand and NIOSH cohorts is presented in Table 1. Risk of diabetes was significantly increased in the “high-exposure” Ranch Hand subcohort.[1] Thus, the NOAEL and LOAEL for the Ranch Hand group are based on the current and initial blood lipid dioxin levels for these groups.[1] Similarly for the NIOSH cohort, the NOAEL is based on the current blood lipid dioxin level (initial level not reported), and the LOAEL is based on the range (mean not reported) of current and

Table 1. Comparison of LOAEL and NOAEL for diabetes

	Ranch Hand		NIOSH	
	Current TCDD, ppt	Initial TCDD, ppt	Current TCDD, ppt	Initial TCDD, ppt
LOAEL	46.2	197.5	>1,500	>11,600
NOAEL	15	52.7	729	Not reported

initial dioxin levels reported for the six people in the highest exposure group who were diagnosed with diabetes. If TCDD exposure were a risk factor for diabetes, it is unlikely that diabetes would not be seen in the NIOSH cohort at a LOAEL of greater than 30-fold that seen in the Ranch Hand cohort.

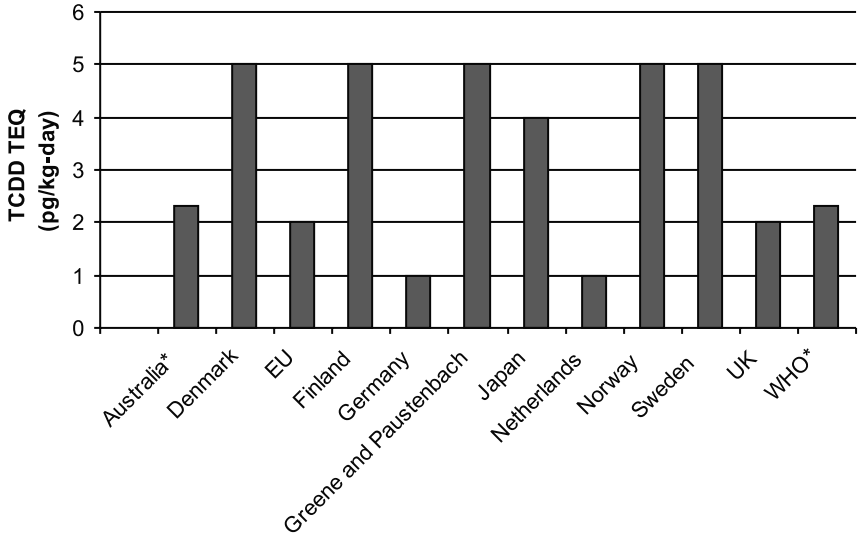
A change in the sex ratio of children born to those in Seveso[2] has been reported. The data suggest a body burden NOAEL of approximately 90 ppt and a LOAEL of 190 ppt based on the mean initial TCDD reported by the authors. A change in sex ratio was also seen in children born to fathers occupationally exposed to 2,4,5-trichlorophenoxyacetic acid and 2,4,5-trichlorophenol (2,4,5-TrCP). Although the authors did not report the TCDD lipid levels, they noted that the gender ratio (males/total births) is 0.38 for exposed fathers but 0.51 for exposed mothers.[3] Interestingly, when the whole cohort of Austrian men exposed to high levels of dioxins at a 2,4,5-TrCP production plant was examined, no difference was seen in sex ratio. However, those fathers who were exposed between the ages of 18 and 20 and between 27 and 29 had more female than male children (4/1 and 4/2, respectively) The other 45 children born to exposed fathers of this cohort included 23 males and 22 females.[4] No significant change in the sex ratio of children born to the Ranch Hand cohort has been seen. However, there were fewer female children born to fathers in the high-dioxin category.[5] This inconsistency among cohorts, along with the inherent instability in sex ratio in small samples, indicates that the findings of Mocarelli et al.[2] should be interpreted with caution.

ENDPOINT WITH STRONG SUPPORT: The most consistently observed effect resulting from exposure to 2,3,7,8-TCDD-contaminated substances in humans is chloracne. Mocarelli et al.[6] described chloracne in people from Zone A in Seveso who had serum 2,3,7,8-TCDD levels ranging from 828 to 56,000 ng/kg lipid-adjusted. The lowest reported 2,3,7,8-TCDD level associated with chloracne was 828 ppt at the time of the accident. In the group that developed chloracne, >95 % were under 20 years old. In fact, children appear to develop chloracne at lower serum 2,3,7,8-TCDD concentrations than adults.[6, 7] Based on the consistent occurrence of chloracne in children with serum 2,3,7,8-TCDD concentrations above 12,000 ppt lipid-adjusted, the clinical relevance, and the ability to examine a sensitive subpopulation, an RfD can certainly be derived for this endpoint.

Recommended RfD for Dioxin

Our review of the available data indicates that chloracne in humans is one endpoint upon which an RfD for dioxin could be established. In support of this RfD, a similar RfD was calculated on the basis of an animal study in which developmental effects was the endpoint.

By using the peak body burden of the child with the lowest serum TCDD concentration (828 ng/kg lipid-adjusted or 166 ng/kg body burden assuming 20 % lipid), and a safety factor of 10 (for conversion from a LOAEL to a NOAEL), an absorbed RfD of 4 pg/kg-day was calculated. Assuming an 80 % bioavailability (EPA default), this equates to 5 pg/kg-day as a dose safe for the development of chloracne, even in children. The true value of the dose that could cause chloracne is probably much



* Promulgated as a tolerable monthly intake, but represented here as a daily intake for comparison purposes. Sources: Australia,[11] EU,[12] UK,[13] WHO,[9] all others.[14]

Figure 1. Comparison of tolerable daily intakes for different countries/regulatory bodies

higher because the chloracne may have been caused by the localized concentrations of TCDD on the skin rather than the systemic body burden. A similar RfD was calculated using developmental effects in rats as an endpoint.[8] Using the approach described here, an RfD of approximately 5 pg TEQ/kg-day would be indicated; this would produce a steady-state body burden in humans of approximately 20 ng TEQ /kg. Moreover, this RfD is similar to the tolerable daily intake suggested by many other regulatory bodies (see Figure 1).

Discussion

This analysis was conducted assuming that the health effects experienced by the various human cohorts were solely due to 2,3,7,8-TCDD because this was the only congener quantified in all of the cohorts. It is known that each of the studied cohorts experienced exposures to other congeners, but because it was impossible to quantify the levels of each congener for which there is a TEF, it was assumed that all effects were solely due to 2,3,7,8-TCDD. Thus, it is likely that the risks calculated from these data sets have been overestimated by at least 10 % to 50 % based on a total TEQ exposure. Therefore, compounding this with the conservative nature by which NOAELs were chosen and safety factors described above were applied, an exposure range of 1-10 pg total TEQ/kg-day should be more than adequate to protect humans from any adverse noncancer effects.

An RfD of 1-10 pg/kg-day based on chloracne in children should be a conservative risk criterion, similar to or higher than current intake levels (depending on data examined), and likely to protect against noncancer effects in almost all people exposed to it. Due to the uncertainty in our knowledge and the less-than-perfect nature of epidemiology studies, it is important to strongly support the

continued reduction of TCDD and other dioxin-like compounds to the environment. Nonetheless, this analysis indicates that current exposure levels should not pose an adverse health risk in the general population. This conclusion is consistent with the conclusions of the World Health Organization[9] report but inconsistent with the EPA[10] view that current uptake in the food could well be hazardous.

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