APPLICATION OF DIOXIN EPIDEMIOLOGY DATA FOR DERIVING TOXICITY VALUES FOR 2,3,7,8-TCDD FOR USE IN RISK ASSESSMENTS

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Introduction

In recent years there has been increased emphasis by the U.S. Environmental Project Agency (EPA) to utilize epidemiological studies rather than laboratory animal studies to derive toxicity values for use in human health risk assessment[1]. In their reanalysis of dioxin toxicity and in response to the National Academy of Sciences (NAS) review and comments[2] on the EPA's 2003 *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds*[3], the EPA derived a reference dose (RfD) using serum TCDD data from the Seveso, Italy population and derived an oral cancer slope factor (CSF) using serum TCDD data from occupational exposure studies conducted in the United States[1]. The objective of deriving RfDs and CSFs is for use in risk assessment where potential hazard and risk associated with exposure to TCDD and dioxin-like compounds (DLCs) can be estimated. Due to the mechanisms by which dioxins are formed and released to the environment during the manufacture of certain chlorinated pesticides (U.S. occupational exposures) and industrial accidents (e.g., Seveso residential exposures), and assuming EPA's toxicity equivalency policy, it is expected that all potential adverse effects are related to the mixture to which human subjects were exposed comprising all DLCs that act through a common mode of action related to the endpoint in question.

The EPA's use of toxicity equivalency factors (TEFs) in the risk assessment framework is based on the concept that all 17 2,3,7,8-substituded dioxin/furan congeners and 12 coplanar polychlorinated biphenyl (PCB) congeners act through a common mode of action mediated by the aryl hydrocarbon (Ah) receptor[1,2,3]. It is therefore critical that dose-response assessments for TCDD and other DLCs consider the dose-response and the contribution of all DLCs to which human subjects were exposed when deriving RfDs and CSFs. Although the NAS criticized the EPA for not adequately addressing background exposures to TCDD and other DLCs, both the NAS and the EPA failed to consider the effect of other DLCs to which Seveso residents or U.S. workers were exposed to as a direct result of the Seveso accident or U.S. occupational exposures, respectively[1,2].

The objective of this paper was to qualitatively evaluate the uncertainties and implications of using only serum TCDD data as an estimate of exposure in the derivation of an RfD and a CSF for TCDD. Our objective was not to provide definitive alternative estimates of the RfD and CSF, or to evaluate the underlying assumptions of the TEFs, but rather to open a dialogue to further consider the appropriateness of deriving toxicity values based on epidemiological studies for a single chemical when there is evidence that the adverse response is actually associated with multiple chemicals (and assuming that each of these chemicals is causally associated with the response).

Materials and Methods

The EPA[1] utilized three key epidemiology studies for deriving two RfDs for TCDD (Baccarelli et al. and Mocarelli et al.)[4,5], and one CSF for TCDD (Cheng et al.)[6]. The focus of this paper is on the two studies used to derive an RfD for TCDD. Based on Mocarelli et al., EPA derived an RfD of 7×10^{-10} mg/kg-day based on their identification of a TCDD lowest adverse effect concentration (LOAEC) of 68 ppt associated with decreased sperm concentrations and motility in male Seveso residents as compared to the Seveso comparison group. Using pharmacokinetic modeling[1], EPA estimated a lowest observable adverse effect level (LOAEL) of 0.020 mg/kg-day. While EPA did not derive an RfD based on Baccarelli et al. (2008), they did estimate a maternal LOAEL for TCDD of 0.024 mg/kg-day based on increased neonatal thyroid stimulating hormone (TSH) concentrations[1]. EPA selected the Mocarelli et al. study

for deriving an RfD because the estimated LOAEL was slightly lower than the LOAEL derived from Baccarelli et al., although they considered the exposure estimates based on Mocarelli et al. to be more uncertain[1].

In evaluating the potential uncertainty and implications associated with deriving a RfD from these studies based only on TCDD, we considered the assumptions of causality inherent to the use of TEFs, the distribution of dioxin congeners reported in trichlorophenol (TCP) solutions and other media related to 2,4,5-TCP manufacturing, the relative toxicity of the 17 2,3,7,8-subsituted dioxin congeners, and the relevance of applying RfDs based on exposure to DLC mixtures to exposures associated with other sources and distributions of DLCs.

Results and Discussion

Exposure to TCDD by the Seveso population was the result of an exothermic reaction within a 2,4,5-TCP reactor that released approximately six tons of material over an approximately 18 km^2 area. Differences in dioxin congener distributions in the 2,4,5-T mixture prior to this reaction as compared to the distribution of dioxin congeners in the released material are uncertain. However, it is very likely that the congener distribution was modified given the exothermic nature of the reaction. For a former 2,4,5-TCP manufacturing facility in Michigan, Collins et al. reported lipid-adjusted serum dioxin congener concentrations for several groups of workers, including those who only worked in the 2,4,5-TCP department[7]. Within the highest exposure group, defined as those exhibiting chloracne, mean lipid-adjusted concentrations were dominated by dioxins with little contribution from furans; the congeners with the highest mean lipid-adjusted concentrations were OCDD, HpCDDs, and HxCDDs, in combination representing over 95 percent of the total contribution. TCDD represented only 0.7 percent of the total 2,3,7,8-substituted dioxin/furan exposure[7].

Warner et al. reported on the dioxin/furan/PCB concentrations for 78 women living within the impacted zone in Seveso at the time of the accident[8]. Similar to the findings of Collins et al.[7], lipid-adjusted serum concentrations for these Seveso residents were dominated by OCDD, HpCDD, and HxCDD congeners (96%) with TCDD only representing 0.02 percent of the total exposure to 2,3,7,8-substituded dioxins/furans. Warner et al. also reported the concentrations for six coplanar PCB congeners[8]. PCB 126 was detected in 91 percent of the samples as compared to TCDD which was detected in only 19 percent of the samples. Furthermore, the mean lipid-adjusted concentration of PCB 126 (55 ppt) was over 30 times higher than that of TCDD (1.6 ppt). These data clearly show that TCDD comprises only a very small proportion (<10%) of the total DLC exposure to Seveso residents.

In addition to the actual lipid-adjusted serum concentrations discussed above, Warner et al. also reported lipid-adjusted toxicity equivalent (TEQ) concentrations for the same set of data[8]. Results indicate that 2,3,4,7,8-PeCDF contributes the greatest proportion to the mean total dioxin/furan TEQ (44%) with TCDD contributing only 12.4 percent to the mean total dioxin/furan TEQ. When coplanar PCBs are also included, PCB 126 provides the greatest proportion to the mean total TEQ (34%) with TCDD contributing only 6.3 percent.

If the TEFs required by EPA accurately explain the relative toxicity of DLCs, then these data clearly show that TCDD is not the major contributing factor to DLC toxicity in Seveso subjects. While TCDD may be viewed as one of several markers of exposure, TCDD concentrations are not the optimal metric for dose-response modeling for the Seveso population. By deriving toxicological criteria using TCDD data only, EPA has overestimated the CSF and underestimated the RfD. One must therefore ponder the relevance of assessing the dose-response relationship for 2,3,7,8-substituted dioxins and furans using only TCDD exposures for either the Seveso population (e.g, RfD) or the U.S. occupational population of 2,4,5-TCP workers (e.g., CSF) when it is clear that these individuals were exposed to a multitude of DLCs that are assumed by EPA to act through the Ah receptor, and where TCDD represents only a very small fraction of the total DLC exposure on both a gross concentration/dose basis and on a TEQ basis. To that

end, what are the critical questions that we should ask when considering TCDD as both the primary marker of exposure as well as the primary causative agent in TCDD epidemiology studies?

1. With TCDD representing only a small fraction of the total TEQ, is it appropriate to use only the TCDD concentration or estimated dose to describe the LOAEL for either reduced sperm concentration/motility or increased TSH concentrations without consideration of the contribution from the other 28 DLCs?

2. Given that different DLC congeners exhibit vastly different Ah receptor binding affinities, would it be expected that different DLC congeners would also exhibit different thresholds to the adverse effects observed in epidemiology studies?

3. Are the potential antagonistic and/or synergistic interactions among the different DLC congeners implicitly accounted for using current dose-response modeling methods?

4. In light of the uncertainty associated with dose-response assessments based only on TCDD from these epidemiology studies, what confidence do we have in EPA's causal analysis of TCDD and classification as a known human carcinogen?

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