

ASSESSMENT OF THE US EPA'S PROPOSED TOXICOLOGICAL VALUES FOR TCDD FOR REGULATION OF DIOXIN-LIKE COMPOUNDS IN FOODS: BRIDGING THE SCIENCE DIVIDE IN A GLOBAL MARKET

Haws LC¹, Fitzgerald L¹, Burkhalter B¹, Harris M², Wikoff DS¹

¹ToxStrategies, Inc. 3420 Executive Center Dr, Suite 114, Austin, Texas, USA

²ToxStrategies, Inc. 23501 Cinco Ranch Blvd, Suite G265, Katy, Texas, USA

Introduction

The U.S. Environmental Protection Agency (USEPA) has recently issued draft toxicological values for TCDD. These values include a chronic oral reference dose (RfD) of 0.7 pg/kg-d and an oral cancer slope factor (OSF) of 0.001 (pg/kg-d)⁻¹. Notably, in developing the OSF, the USEPA concluded that there is no threshold for cancer. The RfD and OSF are relied heavily upon as risk assessment tools, and provide a standard means of evaluating health hazards related to exposures to dioxins in soils, sediments and water, often dictating if remedial actions are necessary. However, the USEPA toxicological values, in particular the OSF, are in stark contrast to those developed by other regulatory and public health agencies around the world. In particular, the World Health Organization (WHO) and Food and Agriculture Organization (FAO) Joint Expert Committee on Food Additives (JECFA, 2001) established a provisional tolerable monthly intake of 70 pg/kg/mo (equivalent to a tolerable daily intake of 2.3 pg/kg/d). The European Commission Scientific Committee on Foods (ECSCF) and the United Kingdom Committee on Toxicity (UKCOT) conducted analyses in the same time frame and came to conclusions similar to those of JECFA, each establishing a tolerable intake rate equivalent to 2 pg/kg/d. Importantly, the JECFA panel of international experts concluded that a tolerable intake could be established for 2,3,7,8-TCDD on the basis of the assumption that there is a threshold for all effects, including cancer. This conclusion was based on substantial evidence demonstrating that the carcinogenicity of 2,3,7,8-TCDD was not linked to mutagenicity or DNA binding, and it occurred at higher body burdens in animals than other toxic effects. As such, the JECFA Committee concluded that the establishment of a tolerable intake based on non-cancer effects would also address any carcinogenic risk.

Given that ingestion of dioxins via food is the major source of exposure to dioxin-like compounds, constituting approximated 95% of total exposure in the U.S., it is informative to evaluate the impact of using the US EPA toxicological values for TCDD to assess the levels measured in foods against the impact of using well-established values developed by other countries. Since 1961, the US Food and Drug Administration (USFDA) has gathered data concerning the levels of dioxin-like compounds in foods as a part of their Total Diet Study (TDS), which is an ongoing market basket study designed to monitor levels of nutrients and contaminants in the U.S. food supply. This study is unique in that prior to testing, foods are prepared as they would be consumed, table-ready, which gives a realistic measure of chemical concentrations in prepared foods actually consumed by the U.S. population. The concentrations of dioxins in food can be used to calculate dietary exposure to dioxins by utilizing consumption information provided by the US Department of Agriculture (USDA) Continuing Survey of Food Intakes by Individuals (CSFII). The US FDA has carried out such calculations, and presents estimates of exposure to PCDDs and PCDFs on a TEQ-adjusted basis.¹ It should be noted, however, that neither the USFDA or USDA use the USEPA toxicity values to set regulatory standards or guidelines for dioxins in foods in the U.S.

The objective of this current analysis was to compare the impact of using the USEPA's draft toxicological values for TCDD to assess the USFDA's exposure estimates to the impact of using the JECFA value. To do so, we first directly compared the daily intake estimates of PCDD/Fs as reported by the USFDA to the USEPA's draft RfD. Second, we conducted standard cancer risk and noncancer hazard calculations using the USFDA exposure estimates. Next, we compared the JECFA value to the daily intake estimates of PCDD/Fs as reported by the USFDA.

Methods

FDA Intake Estimates

Dietary intake estimates for PCDD/Fs from all TDS foods (e.g., dairy, beef, poultry, fats, etc.) collected in 2001-2004 were obtained from the USFDA website². These intakes are based on the average PCDD/F WHO₉₈-TEQ concentrations from composite TDS samples, combined with consumption data for each TDS food as reported in the USDA's CSFII survey. Average PCDD/F sum TEQ concentrations were calculated by USFDA by assigning one of three values to non-detects (ND): zero, 1/2LOD or the LOD. This current analysis focused on intakes associated with TEQ concentrations calculated by applying ND=1/2LOD and ND=LOD. The USFDA presents the intakes by age and sex for 14 different groups. With the exception of the younger age groups (those < 6 yrs) that are not segregated by sex, male and female categories were combined by averaging the two sex-specific intakes in a single age range. USFDA also presents an "all groups" category, which was treated as a sex- and age-adjusted intake over a lifetime in the risk calculations.

Hazard and Risk Calculations

The standard noncancer hazard and cancer risk equations and their default inputs are presented below in Equations 1 & 2, and Table 1, respectively. In estimating non-cancer hazard, three exposure scenarios were assessed: a child (0-6 yrs), adolescent (10-16 yrs) and adult (18-70 yrs). Exposure estimates for each receptor were determined by averaging USFDA intake values from their appropriately defined groups. Specifically, the child-specific exposure value was calculated by averaging exposures from USFDA defined children 2 and 6 yrs of age, the adolescent-specific exposure value was calculated by averaging exposures from USFDA defined children 10 yrs of age and adolescents 14-16 years old, and the adult-specific exposure value was calculated by averaging exposures from USFDA defined adults aged 25-30, 40-45 and 60-65 yrs. We also performed a lifetime hazard calculation using USFDA's age-adjusted exposure value, "all groups." For each receptor, hazard calculations were performed using average exposure estimates calculated with ND samples set to 1/2LOD or the LOD. Additionally, hazard calculations for each receptor were calculated using both the USEPA draft RfD and the JECFA TDI.

Equation 1:

$$\text{Hazard} = \frac{\text{Exposure} \left(\frac{\text{pgTEQ}}{\text{kg-day}} \right) \cdot \text{EF} \left(\frac{\text{days}}{\text{yr}} \right) \cdot \text{ED}(\text{yr})}{\text{AT}(\text{days}) \cdot \text{ToxicityValue} \left(\frac{\text{pgTEQ}}{\text{kg-day}} \right)}$$

Equation 2:

$$\text{Risk} = \frac{\text{Exposure} \left(\frac{\text{pgTEQ}}{\text{kg-day}} \right) \cdot \text{EF} \left(\frac{\text{days}}{\text{yr}} \right) \cdot \text{ED}(\text{yr}) \cdot \text{OSF} \left(\frac{\text{kg-day}}{\text{pgTEQ}} \right)}{\text{AT}(\text{days})}$$

Table 1. Summary of inputs for risk and hazard calculations

		Child	Adolescent	Adult	Age-adjusted
Exposure	pg TEQ/kg-day	derived from US FDA exposure estimates			
EF (exposure frequency)	days/year	365			
ED (exposure duration)	years	6	6	52	70
AT (averaging time)	days	2,190	2,190	18,980	25,550
Toxicity Value - RfD	pg TEQ/kg-day	0.7			
Toxicity Value - TDI	pg TEQ/kg-day	2.3			
OSF (oral slope factor)	(pg TEQ/kg-day) ⁻¹	na	na	na	0.001

na = not applicable

Additionally, the risk equation (Eqn. 2) can be rearranged in order to determine a daily exposure associated with a defined cancer risk level (Eqn. 3). Exposures (i.e., intakes) associated with the OSF at three standard risk levels were estimated: 1 x 10⁻⁴, 1 x 10⁻⁵ and 1 x 10⁻⁶. Other inputs are the same as in the age-adjusted cancer risk equation (Eqn. 2).

Equation 3:

$$Exposure_{RLassociated} \left(\frac{pgTEQ}{kg-day} \right) = \frac{RiskLevel \cdot AT(days)}{EF \left(\frac{days}{year} \right) \cdot ED(years) \cdot OSF \left(\frac{kg-day}{pgTEQ} \right)}$$

Results and Discussion

Estimates of daily dioxin exposure as determined by the USFDA are presented in Figure 1. These levels can be directly compared to the USEPA RfD, to the daily exposures associated with the OSF at three standard risk levels, and to the TDI. When it is assumed that ND values are equal to the LOD, comparisons indicate that the daily exposures to PCDD/Fs in the diet are greater than the RfD for children and adolescents. When it is assumed that ND values are equal to 1/2 the LOD, the daily exposures to PCDD/Fs in the diet are greater than the RfD for children aged 10 and younger. Daily exposures for all age groups greatly exceed the daily intake associated with the draft OSF at all risk levels evaluated. In contrast, all estimates of PCDD/F exposure via the diet are under the JECFA TDI and thus suggest that there is no health concern regarding the consumption of dioxin-like compounds in foods at the levels measured in the USFDA TDS.

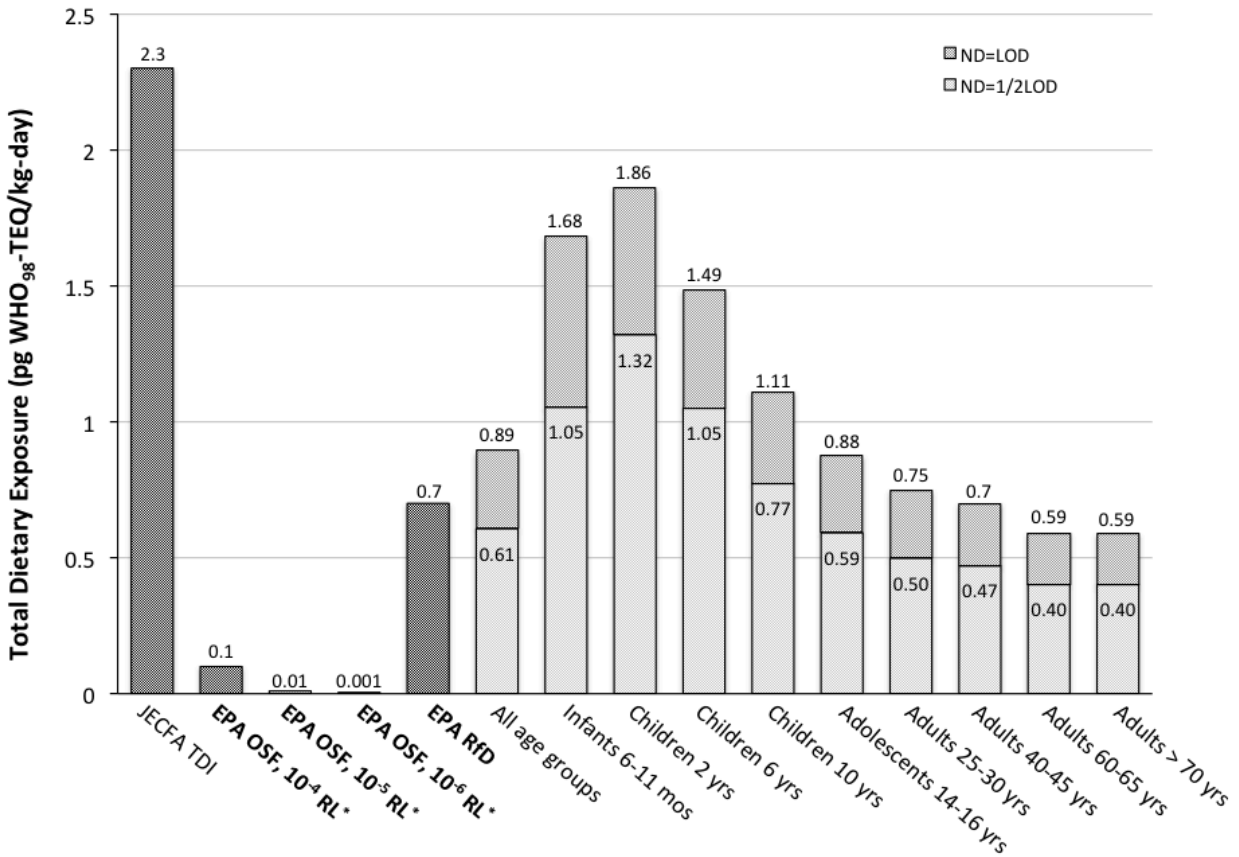


Figure 1. Direct comparison of average estimated dietary dioxin exposures by the US FDA presented alongside exposures corresponding to regulatory values.

*Dose associated with the draft OSF at the specified risk level (RL) – See Eqn. 3

Estimates of non-cancer hazard for the three defined receptors, as well as for the “all groups” combined are presented in **Table 2**. Using the standard USEPA target hazard quotient of 1, data indicate exposures to PCDD/F in foods as measured in the TDS exceeds the USEPA's target hazard quotient for children, adolescents and all groups combined. In contrast, the daily PCDD/F intakes measured in the TDS were below the JECFA TDI for all age groups and, as such, the resulting hazard estimates were all below 1

Table 2. Hazard associated with consuming an average daily diet, calculated using EPA's draft RfD and the TDI

Age Group	FDA Daily Exposure Estimates (pgTEQ/kg-d)		Hazard calculated with USEPA's Proposed RfD		Hazard calculated with JECFA's TDI	
	ND = 1/2LOD	ND = LOD	ND = 1/2LOD	ND = LOD	ND = 1/2LOD	ND = LOD
Child (0-6 yrs)	1.14	1.68	1.63	2.39	0.50	0.73
Adolescent (10-16 yrs)	0.68	0.99	0.98	1.42	0.30	0.43
Adult (18-70 yrs)	0.46	0.68	0.65	0.97	0.20	0.30
Age-adjusted (All groups)	0.61	0.89	0.87	1.28	0.26	0.39

The cancer risk associated with consuming the levels of PCDD/Fs measured in the TDS over a lifetime based on the USEPA proposed OSF was estimated to be 6×10^{-4} or 9×10^{-4} when applying 1/2LOD or the LOD to ND samples, respectively. These estimates are at the upper end of the US EPA allowable risk range. In contrast, as already indicated in Figure 1 above, the JECFA, which is protective of both cancer and non-cancer, indicates that the levels measured in the TDS are below the level of concern for all age groups.

Collectively, these data indicate that conclusions about the mode of action underlying the carcinogenic response to dioxin-like compounds has a profound impact on the specific toxicological values that are derived and these values in turn lead one to substantially different conclusions regarding the levels of dioxin-like compounds in foods. The JECFA value represents consensus of an international panel of experts that there is a threshold for all effects, including cancer, and as such, a single value (provisional tolerable monthly intake) could be developed to protect both cancer and non-cancer. In contrast, the USEPA concluded that the data did not support the idea that a threshold exists for cancer and, as such, developed a toxicological value for cancer that is substantially more conservative than that developed by the JECFA Committee. These differences must be discussed and consensus must be reached to bridge the science divide, thereby facilitating the import and export of foods in a global market.

References

¹US FDA (2010). PCDD/PCDF Exposure Estimates from TDS Samples Collected in 2001-2004. Available: <http://www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/ChemicalContaminants/DioxinsPCBs/ucm077498.htm>. Updated June 2006.

²USDA (2000). United States Department of Agriculture, Agricultural Research Service. Continuing Survey of Food Intakes by Individuals 1994-96, 1998 [CD-ROM]. NTIS No. PB 2000-50027. 2000