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A sensitivity analysis using alternative toxic equivalency factors to estimate U.S. dietary exposures to dioxin-like compounds

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ABSTRACT

EPA recommends sensitivity analyses when applying the toxic equivalency factor (TEF) method to evaluate exposures to dioxin-like compounds (DLCs). Applying the World Health Organization's (WHO) 2005 TEF values and estimating average U.S. daily dietary intakes of 25 DLCs from eight food categories, we estimate a toxic equivalency (TEQ) intake of 23 pg/day. Among DLCs, PCB 126 (26%) and 1,2,3,7,8-PeCDD (23%) dominate TEQ intakes. Among food categories, milk (14%), other dairy (28%), beef (25%), and seafood (18%) most influenced TEQ intakes. We develop two approaches to estimate alternative TEF values. Based on WHO's assumption regarding TEF uncertainty, Approach1 estimates upper and lower TEFs for each DLC by multiplying and dividing, respectively, its individual TEF by ± half a log. Based on compiled empirical ranges of relative potency estimates, Approach2 uses percentile values for individual TEFs. Total TEQ intake estimates using the lower and upper TEFs based on Approach1 were 8 and 68 pg TEQ/day, respectively. The 25th and 75th percentile TEFs from Approach2 yielded 12 and 28 pg TEQ/day, respectively. The influential DLCs and food categories remained consistent across alternative TEFs, except at the 90th percentile using Approach2. We highlight the need for developing underlying TEF probability distributions.

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1. Introduction

Dioxin-like compounds (DLCs), including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and some polychlorinated biphenyls (PCBs), are structurally and toxicologically related halogenated dicyclic aromatic hydrocarbons (USEPA, 2003). DLCs are persistent and lipophilic, bioaccumulating in aquatic and terrestrial food webs. For most people, the principal pathway of exposure to DLCs is ingestion of animal based products (Lorber et al., 2009, 2010; USFDA, 2007).

The World Health Organization (WHO) and the United States (U.S.) Environmental Protection Agency (EPA), among others, recommend using the toxic equivalence factor (TEF) method for evaluating human health risks from exposures to DLC mixtures (USEPA, 2010; Van den Berg et al., 2006). Although the use of whole mixture data or data on a sufficiently similar mixture are preferred risk assessment approaches for environmental mixtures, when data are not sufficient to apply these methods, component-based approaches, such as the TEF method are employed (USEPA, 2000). The TEF method is based on dose addition (USEPA, 2000).

Abbreviations: Cij, DLC average concentrations in each food category; DLCs, dioxin-like compounds; *Eij*, DLC intake estimate for each food category; EPA, U.S. Environmental Protection Agency; f_j, fat fraction estimates for each food category; HpCDF, heptachlorodibenzofuran; HxCDD, hexachlorodibenzo-*p*-dioxin; HxCDF, hexachlorodibenzofuran; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; PeCDD, pentachlorodibenzo-*p*-dioxin; REP, relative estimates of potency; r_j, food ingestion rate for each food category; SI, Supplementary Information; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEF, toxic equivalency factor; TEF_A, alternative TEF value based on the percentile used (e.g., where "A" indicates the percentile—10th, 25th, 50th, 75th, 90th); TEF_B, baseline TEF value; TEF_L, lower TEF value; TEF_U, upper TEF value; TEQ, toxicity equivalence; TEQ_{Aj}, alternative daily TEQ intake rate estimates for the *j*th food category; TEQ_{AT}, alternative total daily TEQ intake estimates; TEQ_L, lower TEQ value; U.S., United States; WHO, World Health Organization.

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After reevaluating the additivity concept for TEFs, WHO's 2005 expert panel on the dioxin TEFs concluded that results from many in vivo DLC mixture studies conducted between 1998 and 2005 were consistent with additivity and supportive of the TEF approach (Van den Berg et al., 2006).

In the TEF method, doses of individual DLCs are scaled based on their toxic potency relative to the index chemical, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). These numerical scaling factors are termed TEFs. TCDD is the index chemical for this class of chemicals because its dose-response behavior is well studied and many studies have compared its toxic potency to that of other DLCs. The product of a DLC's dose and its assigned TEF value is toxicologically equivalent to a dose of TCDD, termed the TCDD toxicity equivalence (TEQ) (USEPA, 2000; USEPA, 2010). The sum of these individual products is the total TEQ (i.e., the TCDD dose that is the toxic equivalent of the DLC mixture dose), presented here as an oral human dose and referred to hereafter as intake. The TEF for each DLC is usually presented as a point estimate. Here, we assess the impact of varying these TEF point estimates.

A WHO expert panel developed the current, consensus TEF values (Van den Berg et al., 2006). In this most recent update of the TEFs, the panelists evaluated data from an empirical range of values developed by Haws et al. (2006) and used expert judgment to assign a final TEF value for each DLC. These ranges were based on a database of in vivo and in vitro studies that compared the toxic potency of individual DLCs to that of TCDD. From each of these comparative toxicity studies, Haws et al. (2006) calculated relative estimates of potency (REPs); the toxicity tests, test conditions, sex, and species used to generate these REPs varied across the DLCs. REP estimates were not weighted based on study type or study quality. The panel assigned TEF values using single point estimates from toxicological studies, rather than specific points within the REP ranges. Typically, the TEF assignment for each DLC was between the 50th and 75th percentiles of the REP range and were generally closer to the 75th percentile to be health protective (Van den Berg et al., 2006). The most recent TEF assignments (Van den Berg et al., 2006) are listed in Table 1 and are referred to as baseline TEF (TEF_B) values.

Here, we developed two approaches to address the sensitivity of TEQ intake to alternative TEF values, as identified in EPA's 2010 TEF document (USEPA, 2010). In the first approach, we considered Van den Berg et al.'s (2006) description of the TEF as a "central value with a degree of uncertainty assumed to be at least ± half a log" and implemented this by estimating upper and lower alternative TEF values by multiplying and dividing each DLC-specific TEF by 3.16 (i.e., "half a log"), respectively (termed "Approach1"). In the second approach, we estimated alternative TEF values using percentile values from the REP data developed by Haws et al. (2006) for each DLC based on the underlying REP empirical range (termed, "Approach2"), using the observed variation as a surrogate for overall uncertainty in the TEF values. When we used the REP empirical range from only the in vivo studies comparing the toxicity of DLCs to TCDD, we termed this "Approach2A"; when we used the REP empirical range from the combined in vivo and in vitro comparative toxicity studies, we termed this "Approach2B".

In this study, we estimated the U.S. daily total TEQ dietary intake from eight food categories to be approximately 23 pg/day using baseline TEF values. Previously, Lorber et al. (2010) estimated that food intakes from these eight categories accounted for approximately 90% (29.8 pg/day) of the U.S. daily total TEQ dietary intake (33.5 pg/day). There are several differences between our analysis and that of Lorber et al. (2010): (1) They included inhalation, soil dermal contact, and water, soil, and vegetable oil ingestion pathways that we did not consider; (2) we evaluated five additional PCBs not included in Lorber et al.; and (3) we used updated DLC concentrations for seafood and eggs as reported by Bolger and Murray (Bolger, P.M., Murray, C., III, Concentrations of dioxin-like compounds in commercial seafood and eggs, 2011, Unpublished results.).

This manuscript focuses on EPA's recommendation (USEPA, 2010) to consider a sensitivity analysis when using the TEF method. Holding constant both the individual DLC concentrations in eight food categories and the daily intake rates of these food categories, we identified the potential ranges of U.S. TEQ exposures from intake of these food categories and examined the influence of alternative TEF values on the TEQ intake estimates associated with intakes of specific DLCs and DLC groups.

2. Materials and methods

To calculate TEQ intake estimates and conduct sensitivity analyses of alternative TEF (TEF_A) values, we needed TEF_A values for each DLC and oral intake estimates (E_{ij}) for each DLC in the eight food categories. This section describes how we obtained values for these factors. Additional information on TEF_A values and the DLC concentrations, food ingestion rates, and fat fraction estimates for each food category is provided in the Supplementary Information (SI).

2.1. Oral DLC intake estimate (E_{ij})

For the ith DLC (for $i = 1, 2, \ldots, n$) and jth food category (for $j = 1, 2, \ldots, m$), oral DLC intakes (E_{ij}, pg/day) were estimated as the product of DLC average concentrations in food (C_{ij}, pg/g), food ingestion rate (r_j, g/day), and the total fat fraction (f_j) using the following Eq. (1).

$$E_{ij} = C_{ij} \times r_j \times f_j \quad (1)$$

2.2. DLC concentrations in U.S. foods (C_{ij}, pg/g)

Table A.1 in the SI summarizes DLC average concentrations (pg/g) in the following eight food categories: milk, other dairy (e.g., cheeses, yogurt), beef, poultry, pork, other meats (e.g., unidentified meat in casseroles), eggs, and seafood, based on U.S. estimates. From Lorber et al. (2009, 2010), we obtained DLC concentrations for all food categories except seafood and eggs (Bolger, P.M., Murray, C., III, Concentrations of dioxin-like compounds in commercial seafood and eggs, 2011, Unpublished results.). Lorber et al. (2010) assumed that DLC concentrations reported as below the detection limit in individual food samples were present at concentrations equal to one-half the detection limit. They also evaluated trends in DLC exposures over time and limited their analyses to DLCs for which concentration data were available over relevant time periods. Lorber et al. (2010) included many dioxins and furans for which TEF values had been developed. Although concentration data were available for eight PCBs, they identified only three (PCB 77, PCB 126, and PCB 169) that were consistently reported in all food categories and limited their analysis to these three PCBs. In our analysis, we included the additional concentration data for PCB 81, PCB 118, PCB 105, PCB 156, and PCB 157 that were available for some food categories. We did not evaluate the variance of any DLC concentrations in the food categories due to our focus on TEF uncertainty.

2.3. Food ingestion rate (r_j, g/day)

The food ingestion rates (g/day) for each food category (r_j) are milk (175 g/day), other dairy(55 g/day), beef (49.7 g/day), pork (15.4 g/day), poultry (35 g/day), other meats (24.5 g/day), eggs (16.8 g/day), and seafood (15.5 g/day). These rates are based on