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Uncertainty analysis in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) cancer dose–response for three occupational cohorts

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ABSTRACT

While the U.S. EPA has issued a draft report with a 1% TCDD effective dose (ED_{01}) of 87.9 pg/kg/day based on continuous integration of key scientific evidence, a detailed and comprehensive uncertainty analysis has not been well documented. In this study, a new estimate for ED_{01} was derived based on uncertainty analysis by quantitatively assessing the potential bias arising from the selection of kinetic models, dose–response models and cohorts. The cumulative serum lipid concentration (CSLC) and cumulative body burden (CBB) were reconstructed as dose metrics using a concentration- and age-dependent pharmacokinetic model (CADM), physiologically based pharmacokinetic model (PBPK), and age-dependent half-life model (FV), and the reconstructed dose metrics based on CADM and PBPK were generally higher than those based on the FV model. Three dose–response curves (linear, multiplicative and power) were used to link dose metrics and cancer risk to estimate ED_{01}, and the linear model resulted in the lowest ED_{01}, followed by the power model and multiplicative model, for the same cohort. Meanwhile, ED_{01} based on the CADM model was the highest, followed by those based on the PBPK model and first-order model. Finally, the ED_{01} was estimated to be 17.03 ± 7.83 pg/kg/day by statistically analyzing the distribution of ED_{01} values based on various kinetic models, cohorts and dose–response models. The study presented here strengthens the scientific basis for understanding the potential health implications of TCDD exposure.

1. Introduction

In 1985, the U.S. Environment Protection Agency (EPA) classified 2,3,7,8-TCDD as a probable human carcinogen based on animal carcinogenicity evidence (U.S. EPA, 1985). Later, data from a number of epidemiological studies strongly and consistently demonstrated the association between TCDD exposure and cancer risk (Becher et al., 1998; Crump et al., 2003; Flesch-Janys et al., 1998; Ott and Zober, 1996; Steenland et al., 1999). Together with the carcinogenicity evidence from multiple species, mode of TCDD carcinogenicity (aryl hydrocarbon receptor (AhR)-promoter), and the similarity between human and animal AhR, the U.S. EPA concluded that TCDD was "best characterized as carcinogenic to humans" in 2003 (U.S. EPA, 2003). In 2010, the U.S. EPA issued a draft report with a 1% effective dose (ED_{01}) (87.9 pg/kg/day), the dose that would increase the lifetime risk of cancer (all kinds) mortality by 1% due to the lifetime exposure to TCDD, based on the National Institute for Occupational Safety and Health (NIOSH) cohort (Cheng et al., 2006; U.S. EPA, 2010); however, the U.S. EPA did not provide a detailed and comprehensive uncertainty analysis for ED_{01} evaluation across kinetic models and dose–response models (U.S. EPA, 2010, 2012).

Besides the NIOSH cohort, there are two other critical epidemiologic cohorts, the BASF cohort and the Hamburg cohort, which have also usually been used for the development of dose–response relationships using a first-order kinetic model with constant elimination rate (FC) (Becher et al., 1998; Flesch-Janys et al., 1998; Ott et al., 1993; Ott and Zober, 1996; Zober et al., 1990). For all three cohorts, only the measured blood concentration at the end of follow-up is available, while the cancer risk of TCDD is associated with the lifetime-cumulative exposure. Thus, re-construction of dose metrics regarding exposure and follow-up period is essential for establishing a dose–response relationship. In the earlier dose–response assessment, the FC model was applied to reconstruction of the dose metric (Becher et al., 1998; Crump et al., 2003; Ott and Zober, 1996; Steenland et al., 2001). However, the FC model is not supported biologically, since an inducible elimination rate has been observed in rodents and humans (U.S. EPA, 2010). Growing evidence shows that high-dose TCDD sequesters in the liver, because TCDD induces cytochrome P450 1A2 (CYP1A2) that can bind with TCDD, therefore leading to an elevated elimination rate (Aylward et al., 2005a; Aylward et al., 2005b; Emond et al., 2006; Milbrath et al., 2009). A number of kinetic models have been developed to describe the inducible elimination rate of TCDD, including the concentration- and age-dependent pharmacokinetic model (CADM) (Aylward et al.,

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2005a; Aylward et al., 2005b) physiologically based pharmacokinetic model (PBPK) (Emond et al., 2004; Emond et al., 2005; Emond et al., 2006; U.S. EPA, 2010) and first-order model with age-dependent half-life model (FV) (Milbrath et al., 2009). The estimated ED_{01} is largely dependent on reconstruction of dose metrics based on the selection of kinetic models; for example, ED_{01} was found to be 18.6 pg/kg/day when using the FC model for the NIOSH cohort, much lower than that (87.9 pg/kg/day) derived using CADM (U.S. EPA, 2003). Thus, the potential bias from the selection of kinetic models should be quantitatively assessed.

In addition, the selection of models for developing a dose–response relationship is one of the uncertainty factors, since even the 'best' model is probably not ideal (Becher et al., 1998; Starr, 2001). The multiplicative model has been employed to evaluate ED_{01} in the latest draft from EPA, while the utilization of both linear and non-linear models for deriving dose–response relationships has been recommended by the EPA Science Advisory Board (SAB) (U.S. EPA, 2010). Different models for establishing dose–response relationships can lead to significantly different ED_{01} values, as exemplified by the substantially different ED_{01} values for the Hamburg cohort: 6 ng/kg, 18.2 ng/kg, and 32.2 ng/kg when using power, additive and multiplicative models, respectively (Becher et al., 1998; U.S. EPA, 2003). Therefore, a detailed and comprehensive uncertainty analysis for ED_{01} evaluation should consider the selection of dose–response models (U.S. EPA, 2010, 2012).

The objective of this study is to provide a daily-intake ED_{01} based on a comprehensive uncertainty analysis by considering the bias from the selection of cohorts, kinetic models, and models for establishing the dose–response relationship. The results presented here strengthen the scientific basis for understanding the potential health implications of TCDD exposure and help assess and manage the risk from TCDD.

2. Materials and methods

2.1. Procedure for estimating ED_{01}

Three epidemiological cohorts, including the NIOSH cohort, BASF cohort, and Hamburg cohort, were used in this study. As shown in Fig. 1, the procedure for estimating ED_{01} consisted of four steps. First, the cohort characteristics, including sample size, measured serum lipid TCDD concentration, standardized mortality ratio (SMRs) for all combined cancers, mean duration of occupational exposure (MDE), and mean years of follow-up (MYF) were retrieved from the literature. Second, a dose–response relationship between TCDD exposure and cancer risk was developed. In this step, the dose metric was back-calculated using four kinetic models including the FC model, FV model, CADM model, and PBPK model (Aylward et al., 2005a; Aylward et al., 2005b; Emond et al., 2004; Emond et al., 2005; Emond et al., 2006; Milbrath et al., 2009; U.S. EPA, 2012), and three dose–response models were employed to link dose metric and response. Using the dose–response curves developed in Step 2, ED_{01} was estimated in Step 3. Finally, robustness analysis was performed to address the heterogeneity in the dose–response development (Step 4 in Fig. 1).

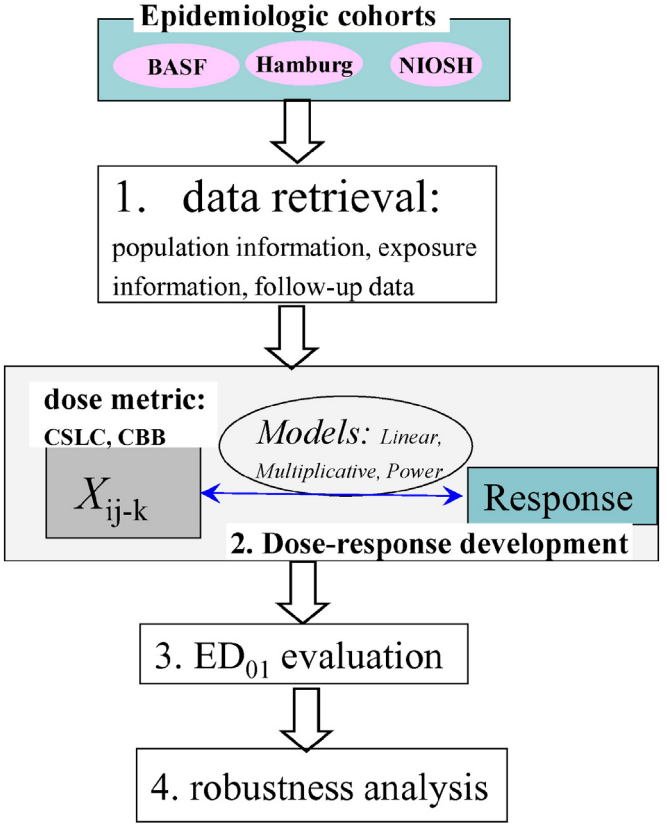

Fig. 1. Framework for the evaluation of 1% effective dose (ED_{01}) for human exposure to TCDD. Abbreviations: *X*, dose metric; *i*, *j*, and *k* are the indexes for cohorts, kinetic models and dose metrics; CSLC, cumulative serum lipid concentration; CBB, cumulative body burden.

2.2. Development of dose–response relationship

2.2.1. Back-calculation of dose metrics

In previous studies, there has been no uniform standard for selecting a biomarker as dose metric. For example, body burden has been selected in the report of the U.S. EPA (U.S. EPA, 2000), while the serum (blood) lipid concentration was applied for the NIOSH and Hamburg cohorts, respectively (Flesch-Janys et al., 1998; Steenland et al., 2001). Thus, considering that different dose metrics have been used in previous reports, the cumulative serum lipid concentration (CSLC) and cumulative body burden (CBB) were both selected as dose metrics to address the uncertainties in estimating ED_{01}.

In the FC and FV models, it is assumed that all dioxins are sequestered in lipid, and that the ratio of TCDD concentration between body burden and lipid is a constant, usually 0.25. Thus, the dose–response relationships based on both CSLC and CBB should be the same. In CADM and PBPK models, this ratio varies with concentration and age. Therefore, there are six dose metrics including CSLC in the FC and FV models, and CSLC and CBB in the CADM and PBPK models.

An illustration for the back-calculation of dose metrics is shown in Supplementary material Fig. S1. For the back-calculation of dose metrics, the serum TCDD lipid concentrations ($STLs_{end}$) that were measured at the end date of follow-up studies in epidemiological studies is essential (Flesch-Janys et al., 1998; Steenland et al., 2001), however, previous papers did not provide $STLs_{end}$. Fortunately, the CSLC estimated from $STLs_{end}$ using the FC model for all the subgroups of the three cohorts were reported in previous studies (Crump et al., 2003; Flesch-Janys et al., 1998; Steenland et al., 2001). Thus, the $STLs_{end}$ for each subgroup of three cohorts can be back-calculated using reported CSLC values by the following equation.

$$STLs_{end} = f^{-1}(CSLC, et, fut, halflife) \quad (1)$$

where *et*, *fut*, and *halflife* represented MDE (years), MYF (years) and half-life (years), respectively (Table 1), and *f* represents the FC model. Then STLs and body burden (BB) for all times ($STLs_{-t}$ and BBs_{-t}) of the whole period (including both the exposure period and follow-up period) were estimated from the $STLs_{end}$ using Eq. (2).

$$(STLs_{-t}, BB_{-t}) = k^{-1}(STLs_{end}, et, fut, age, t) \quad (2)$$

where *age* was the age of workers for first exposure (AFE in Table 1), and *k* was the kinetic model applied, including the FV, CADM, and