DEVELOPMENT OF A DIRECT CONTACT CRITERION (DCC) FOR 2,3,7,8-TCDD TEQ IN SOIL USING DETERMINISTIC AND PROBABILISTIC METHODS

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Introduction

For many years, a soil criterion value of 1 ug/kg (ppb) was established for dioxin like compounds expressed as toxic equivalents (TEQ) of 2,3,7,8-tetrachlorodibenzodioxin (TCDD). This value has been used for environmental regulation of many solid waste sites[1]. This criterion is based on a virtually safe dose (VSD) that considered both carcinogenic and non-carcinogenic endpoints established in 1984[2]. In 2006, a new analysis performed using probabilistic risk methods and more up to date toxicity information confirmed that the value of 1 ppb was health-protective criterion for both carcinogenic and non-carcinogenic endpoints[3]. In this paper, we use deterministic and probabilistic methods and site-specific information to derive a range of residential direct contact criteria (DCC) for TCDD TEQ in soil for potential use in the assessment of soils in Midland, MI. The methods and assumptions used in this derivation address many of the issues raised by EPA's Science Advisory Board (SAB) and the National Academy of Science (NAS) in their reviews of EPA's Dioxin Risk Assessment[4,5,6].

$$DCC_c = \frac{TR \cdot AT_c \cdot 1x10^{-9\ \mu g/kg}}{SF \cdot \left(EF_i \cdot IF \cdot AE_i + EF_d \cdot DF \cdot AE_d\right)} \quad \text{(Eq. 1)}$$

$$DCC_{nc} = \frac{THQ \cdot RfD \cdot AT_{nc}}{EF_i \cdot IF \cdot AE_i + EF_d \cdot DF \cdot AE_d} \quad \text{(Eq. 2)}$$

DCC =Direct contact criterion (ug/kg)
EF_i = Ingestion exposure frequency (day/yr)
TR = Target risk level (unitless)
AE_i = Ingestion absorption efficiency (percent)
AT_c = Averaging time for carcinogenic effects (days)
EF_d = Dermal exposure frequency (day/yr)
SF = Cancer Slope Factor $(mg/kg\text{-}day)^{-1}$
DF = Age-adjusted soil dermal factor (mg-yr/kg-day)
IF = Age-adjusted soil ingestion factor (mg-yr/kg-day)
THQ = Target Hazard Quotient (unitless)
AE_d = Dermal absorption efficiency (percent)
RfD = Oral reference dose (mg/kg-day)
AT_{nc} = Averaging time for noncarcinogenic effects (days)

Materials and Methods

For carcinogenic effects, eq. 1 was used and for noncancer effects, eq. 2 was used. The target risk level (TR) was 1 in 100,000 and the target hazard quotient (THQ) was 1. The averaging time for carcinogenic efects was 75 years or 27,375 days for both the deterministic and probabilistic calculations. The averaging time for non-carcinogenic effects was 30 years or 10,950 days for the deterministic calculation and the exposure duration in days for the probabilistic calculation.

Variability in Exposure Factors

1) Exposure Frequency (EF)

For EF_i and EF_d, a value of 245 days/yr was used in the deterministic calculation and a normal distribution with a mean of 209.8 days/yr and a standard deviation of 19.4 days/yr was used in the probabilistic calculation. This distribution was derived from default values and climate data in Midland[7,8].

2) Exposure Duration (ED)

For the deterministic calculation, default values of 6 years and 24 years were used for the child and adult respectively[8]. For the probabilistic calculation, the interindividual variation in duration were modeled using the approach of Johnson and Capel[9] and recent US Census data on the rate of moving out of the original county of residence in the Midwest[10].

3)Body Weight (BW)

For the deterministic assessment, default body weight values of 15 kg for 0-6 years and 70 kg for 6-30 years were used[8]. For the probabilistic assessment, age-specific body weight distributions were defined for various age groups. One year age groups were used for ages 0-19 and the age groupings of 19-25, 25-35, 35-45, 45-55, 55-65 and >65 were used for older individuals. Correlation coefficients of 0.95 were assumed for body weights from one age group to the next to best represent transitions in body weight from one age group to the next, consistent with the known variation in patterns of growth across children [11].

4) Age-Adjusted Soil Ingestion Factor (IF)

The calculation required age-specific body weights and soil ingestion rates. IF was developed using eq. 3. For the deterministic calculation, a soil ingestion rate for children of 92.2 mg/day was used[12]. For adults, a soil ingestion rate of 46.1 mg/day was used[13]. For the probabilistic calculation, the distribution of the child soil ingestion rate was represented by a mixture of two lognormal distributions, and parameters were obtained by maximum likelihood. For the probabilistic calculation, in each iteration of the simulation, the adult soil ingestion rate was calculated as one half of the value drawn from the distribution of childrens' soil ingestion rates. This procedure maintained the relative relationship between adult and child rates assumed for the deterministic assessment. By linking the adult ingestion rate directly to the child ingestion rate, a perfect correlation is assumed, although these factors may be independent.

$$IF = \frac{IR_{child} \cdot ED_{child}}{BW_{child}} + \frac{IR_{adult} \cdot ED_{adult}}{BW_{adult}} \quad \text{(Eq. 3)}$$

IR_x = Soil Ingestion Rate (mg/day)
ED_x = Exposure Duration (yr)
BW_x = Body Weight (kg)

5) Ingestion Absorption Efficiency (AE_i)

AE_i values were developed from a bioavailability study of Midland soils conducted in rats and swine[14]. A value of 25% was used for the point estimate calculation. A lognormal distribution with a mean of 23% and a standard deviation of 6% was used for the probabilistic calculation.

6) Age-Adjusted Dermal Factor (DF)

For both the deterministic and probabilistic calculations, the DF is calculated using Eq. 4. The Adherence Factor (AF) is the amount of soil that adheres to the skin. For the deterministic calculation, the AF values used were 0.07 mg/cm^2 and 0.2 mg/cm^2 for adults and children respectively[15,16]. For the probabilistic calculation, raw data on soil adherence were obtained from Dr. John Kissel of the University of Washington, lognormal distributions of soil loading on various parts of the body (hands, arms, legs, faces and feet) were developed and weighted according to the fractions of total body surface area represented by these parts[15,16]. The resulting lognormal distribution has an arithmetic mean of 0.14 mg/cm^2 and an arithmetic SD of 0.27 mg/cm^2.

$$DF = \frac{SA_{child} \cdot EF \cdot AF_{child} \cdot ED_{child}}{BW_{child}} + \frac{SA_{adult} \cdot EF \cdot AF_{adult} \cdot ED_{adult}}{BW_{adult}} \quad \text{(Eq. 4)}$$

SA_x = Skin Surface Area Exposed (cm^2)
EF = Exposure Frequency (days/yr)
AF_x = Adherence Factor (mg/cm^2)
ED_x = Exposure Duration (yr)
BW_x = Body Weight (kg)

7) Exposed Skin Surface Area (SA)

For the deterministic calculation, exposed skin areas of 5800 cm^2 and 2670 cm^2 were used for adults and children respectively[8,15,16]. Because body weight and skin surface area are highly correlated, in the probabilistic calculation, the total skin surface areas for both adults and children were calculated from body weight[17]. The fraction of total skin area exposed was treated as uniform distributions from 0 to 0.32 for adults and from 0 to 0.42 for children. These maximum values corresponded to the values used in the deterministic calculation.

8) Dermal Absorption Efficiency (AE_d)

For the deterministic calculation, a value of 1.75% was used, the midpoint of a range of measurements[18]. For the probabilistic calculation, these data were fit to a lognormal distribution with a mean of 1.2% and an SD of 0.019.

Variation and Uncertainty in Toxicity Criteria

A threshold, non-linear mode of action for tumors induced by dioxin is supported by a large body of scientific evidence, as reflected in the recommendations of the SAB and the NAS to USEPA[4,5]. The overwhelming consensus is that binding of dioxin to the aryl hydrocarbon receptor is initial key event and pivotal component for dioxin-induced events[19,20]. A dose-response assessment for dioxin based on receptor binding would predict a nonlinear dose-response relationship with a threshold for tumor induction. A nonlinear relationship is more consistent with the available chronic animal bioassays and human epidemiology studies[19]. For this reason, a non-linear threshold toxicity criterion, i.e. a reference dose, is most appropriate for developing the direct contact soil criterion, in contrast to the traditional linear approach of using a cancer potency factor for carcinogens.

However, for comparison purposes, both a non-linear approach and a linear approach are presented here. The recent NTP bioassay for TCDD provided the dose response data. The critical effect from the bioassay was the occurrence of liver adenomas[21]. Benchmark dose modeling was used to obtain a point of departure (POD)

value for TCDD concentrations in the rat liver at the 1% response level (EC_{01}) and its 95% lower confidence limit (LEC_{01}). This range of the LEC_{01} in the rat liver was 1.97 - 7.71 ng/g[21]. Using a human PBPK model, an external dose in humans that would result in similar concentrations in the liver was determined to be 3.3 - 12.9 ng/kg-day[21]. The value of 3.3 ng/kg-day was used here; this is the lowest (most health-protective) estimate of the external dose in humans corresponding to the 1% response rate.

1) Reference Dose for Carcinogenic Effects of TCDD TEQ

A reference dose was derived using eq. 5. The default value of 10 for UF_a (interspecies extrapolation) is comprised of values of 3.16 (square root of 10) for toxicokinetic variation and 3.16 for toxicodynamics variation. For the deterministic assessment: (1) the toxicokinetic component of UF_a was set equal to 1.0, since a PBPK model was used to account for species differences; and (2) for the toxicodynamic component, the health protective value of 1.0 was used even though there are numerous data that suggest humans are at least a factor of 10 less sensitive than rats to the effects of dioxin because of lower affinity of the human AHR[19,20]. For the probabilistic assessment: (1) the UF of 1.0 was retained for the toxicokinetic component; and (2) the UF for the toxicodynamic component was allowed to range from 0.1 to 1.0 as a uniform distribution.

$$RfD = \frac{POD}{UF_a \cdot UF_h \cdot UF_s \cdot UF_. \cdot UF_d} \quad \text{(Eq. 5)}$$

RfD = Reference Dose (mg/kg-day)
POD = NOAEL, LOAEL or BMD (mg/kg-day)
UF = Uncertainty Factors (see text)

UF_h is intended to cover potentially sensitive human subpopulations. The default value of 10 for UF_h (intraspecies extrapolation) is comprised of values of 3.16 (square root of 10) for toxicokinetic variation and 3.16 for toxicodynamic variation. For the deterministic assessment, a value of 3.16 was adopted for the toxicokinetic component to account for individual variation in TCDD half-life and a conservative value of 3.16 was retained for the toxicodynamic component to account possible variation in sensitivity between individuals. Hence, the net UF_h value was 10. For the probabilistic assessment, 1) the toxicokinetic component was defined as a uniform distribution ranging from 1.0 to 3.16 to account for possible variation in the TCDD half life and 2) the toxicodynamic component was also defined as a uniform distribution ranging from 1.0 to 3.16 to account for the fact that AHR polymorphisms do not affect binding of the ligands to the receptor[21].

For the deterministic calculation, the value of 3 was used for UF_l (LOAEL-to-NOAEL extrapolation) to ensure that the resulting cancer RfD did indeed fall below the threshold for tumor formation. For the probabilistic calculation, this value of UF_l was allowed to range from 1.0 to 10 because of uncertainty over the location of the threshold relative to the POD. For UF_s (subchronic-to-chronic extrapolation), a value of 1 was used because the key study included lifetime exposures. For UF_d (database insufficiencies), a value of 1 was also used because TCDD is extremely well studied.

A value of 30 (1 x 10 x 1 x 3 x 1) was adopted for the net uncertainty factor in the deterministic assessment resulting in a cancer reference dose of 0.11 ng/kg-day. For the probabilistic assessment, dividing the distribution of POD values by the distributions of uncertainty factors resulted in a distribution of cancer reference dose values that were approximately lognormal distribution with an arithmetic mean of 1.1 ng/kg-day and an arithmetic standard deviation of 1.5 ng/kg-day.

2) Cancer Potency Factor for TCDD TEQ

A linear cancer potency factor was calculated by dividing the response rate (1%) by the POD. For the deterministic calculation, the response rate of 1% divided by the human-equivalent LED_{01} value of 3.3 ng/kg-day yielded a value of 3000 per mg/kg-day. For the probabilistic calculation, dividing 1% by the distribution of POD values yielded a distribution of cancer potency factors that was approximately lognormal with an arithmetic mean of 1790 per mg/kg-day and an arithmetic standard deviation of 648 per mg/kg-day.

3) Non-cancer Toxicity Criterion for TCDD TEQ

The critical non-cancer effect of TCDD was a reduction in body weight observed in Wistar-Han rat pups on postnatal day 4[23]. The dose measure used was peak maternal body burden during gestation. These continuous data were fit to a Hill dose-response model with the POD defined as a change of 1 control SD from the control mean response. The benchmark dose (BMD) and its lower confidence limit (BMDL) using maternal body burden as a dose metric were 99.4 and 67.0 ng/kg respectively. For the deterministic calculation, a one compartment pharmacokinetic model with a half-life in humans of 2774 days was used to estimate human equivalent doses of 0.031 and 0.021 ng/kg-day corresponding to the BMD and BMDL respectively. For the

deterministic assessment, UF_h was set at 10 to account for both toxicokinetic and toxicodynamic variation. All other UF values were set to 1.0, yielding a net UF of 10 and an RfD value of 2.1 pg/kg-day. For the probabilistic assessment, the dose at the 1% POD was represented by a lognormal distribution with an AM of 0.031 ng/kg and a 5th percentile value of 0.021 ng/kg-day. The toxicodynamic component of UF_a was varied from 0.1 to 1 and the toxicodynamic component of UF_h was varied from 1 to 3.16. All other UF values were set to one. The resulting RfD was represented by a lognormal distribution with an AM of 22 pg/kg-day and an ASD of 20 pg/kg-day.

Results and Discussion

Cancer

The DCC for TCDD TEQ resulting from the deterministic calculation using the cancer RfD was 250 ppb. That resulting from the deterministic calculation using the linear cancer potency factor was 19 ppb. The range from the 5th to 95th percentiles from the probabilistic calculation was 410 – 68,000 ppb (mean = 17,000 ppb) using the threshold cancer RfD and 54 – 3500 ppb (mean = 920 ppb) using the linear cancer potency factor.

Noncancer

The DCC resulting from the deterministic calculation using noncancer toxicity criterion was 4.8 ppb. The range from the 5th to the 95th percentiles from the probabilistic calculation was 13 – 1400 ppb (mean = 370 ppb).

These values are all larger than the value of 1 ppb commonly used for regulation [1,2,3]. In the DCC derivation based on the linear cancer potency factor, the soil ingestion rate and exposure duration were the most influential variables. In the derivation based on the nonlinear cancer RfD, the RfD and the soil ingestion rate were most influential. In the derivation based on noncancer effects, the soil ingestion rate and the developmental RfD were most influential.

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