

## An Approach to Calculating Childhood Body Burdens of Dibenzodioxins and Dibenzofurans Which Accounts for Age-Dependent Biological Half Lives

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### Introduction

Substantial debate continues regarding the appropriate noncancer reference dose assumptions to use when conducting a risk assessment of dioxin. Much of this concern is centered on limited research and speculation regarding noncancer health effects in infants, young children and the fetus (in utero). For example, the intake of dioxin due to breast feeding may exceed the background dietary dose in adults by an order or magnitude or more during certain time periods within the first 6-12 months after birth. Also, estimates of upper bound soil ingestion and dermal contact with dioxins among young children (ages 0-7) can readily exceed the chronic tolerable daily intake levels (1 to 4 pg/kg-day) proposed by some U.S. and international regulatory/advisory groups<sup>1,2,3,4</sup>. Despite trends showing decreasing body burdens of dioxins in developed countries over the past two decades<sup>5</sup>, some researchers suspect that total dietary intake of dioxin-like compounds in many children and adults may already exceed this tolerable intake range without considering any specific local sources like dioxins in residential soils<sup>6,7</sup>.

To a large extent, our concerns about the potential health effects of dioxins in humans are due to the high estimated daily doses to breast-fed infants and other childhood exposures that are speculated to lead to subtle reproductive and development effects. USEPA<sup>7</sup> and other regulatory/advisory groups<sup>1,2,3</sup> generally agree that one reasonable dose metric for comparison of dioxin dose-response across species is steady state body burden (i.e., ng dioxin per kg body weight; or pg/g lipid, or parts per trillion or ppt). For the most sensitive animal reproductive toxicity studies relied upon to develop the current tolerable daily intakes, the estimated equivalent human body burden of dioxins appears to be within 10- to 50-fold of average background levels for dioxin body burdens in the general population<sup>7</sup>. Since the (Ah-receptor dependent) mechanism of dioxin toxicity is thought to be a key component in determining health risks of dioxin-like compounds and the half life of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in humans is much longer than that in rodents, the occurrence of body burdens in the general population that are close to adverse effect levels in the animal studies is a significant concern<sup>7</sup>. However, there are many unanswered

questions regarding human responses to these apparently receptor-dependent mechanisms, including our poor understanding of response thresholds, pharmacokinetics and pharmacodynamics of TCDD in humans, and the influences of antagonism, potentiation or synergism by the many known Ah receptor binding compounds in the environment and our daily diet<sup>1,2,3,8</sup>.

Body burden measurements (in adipose tissue) in a series of 20 Hamburg infants by Kreuzer et al.<sup>9</sup> have suggested that the high daily dioxin doses from breast feeding may not lead to the high body burdens expected (because most scientists have assumed nearly complete absorption and a constant half-life for all ages). Using a simple pharmacokinetic model keyed to age-dependent adipose tissue volume, Kreuzer et al obtained a reasonable fit with the body burden data of 20 Hamburg infants and a 4 year-old child from the Seveso incident. The model indicated that the half life for TCDD in infants may be only 5 to 6 months, much shorter than the 7 to 11 years estimated for adults. These age-dependent half life findings may have broad implications for interpreting body burden estimates and dose-response for dioxins in infants and young children.

The purpose of this study is to apply an age-dependent half life model to examine the range of child (ages 0-7) body burdens that correspond to selected exposure scenarios involving background dietary and environmental doses of dioxins. The scenarios examined include breast-fed and non-breast-fed infants feeding for 6 months, other dioxin uptake from foods through age 7, and exposures to urban residential soils at 1 ppb TCDD toxic equivalents (TEQ). These body burden estimates in children are then compared to the adult body burden estimates corresponding to the range of tolerable daily intakes (1 to 4 pg TEQ/kg-day) proposed by some U.S. and international regulatory/advisory groups<sup>1,2,3,4</sup>.

## Methods and Materials

A simple spreadsheet model was adapted from the toxicokinetic model for TCDD described by Kreuzer et al.<sup>9</sup>. The model is dependent on two major components. First, the model assumes that the volume of distribution for dioxins is exclusively the volume of total body fat in humans. This volume expands substantially during childhood and tends to reduce the effective half life of dioxins at early ages. Second, these authors proposed that an equilibrium may exist between ingested/excreted dietary fats and the body burden of dioxins, particularly for infants and young children. Since more dietary fat is taken in by breastfed infants, and a greater proportion of dietary fat is excreted in these infants, the net body burden in infants may be attenuated compared to adult uptake.

Table 1 presents the model parameters for children from birth through age 7. Body weights and fat volumes for males were derived from USEPA<sup>10</sup> and ICRP<sup>11</sup>, respectively. Half life values at various ages were calculated using an algorithm relating them to the body fat volume. The algorithm for TCDD (Half life =  $85.58 + 187.29 * \text{Fat volume}$ ) is derived from the half life and fat volume values for an infant (5 months and 0.36 kg) and an adult (9.5 years and 18.06 kg). Based on longitudinal blood measurements in a Yucheng patient presented by Masuda<sup>12</sup> for selected dibenzofuran congeners (PeCDF, HxCDF, and HpCDF), it was assumed that age-dependent half life would increase 10% from that calculated for TCDD for each additional chlorine atom on the 2,3,7,8-TCDD nucleus.

**Table 1. Age-Dependent Half Life Model Parameters**

Age (years)	Body	Adipose	Adipose	TCDD	Rate Constant			
	Weight (kg)	Volume (%BW)	Volume (kg)	T-1/2 (days)	TCDD/F	PeCDD/F	HxCDD/F	HpCDD/F
0	3.27	11.0	0.36	153	0.00453	0.00408	0.00362	0.00317
0-0.5	5.56	11.0	0.61	200	0.00346	0.00312	0.00277	0.00242
0.5-1	9.00	11.2	1.01	274	0.00253	0.00227	0.00202	0.00177
1-2	11.37	11.5	1.31	330	0.00210	0.00189	0.00168	0.00147
2-3	13.64	12.0	1.64	392	0.00177	0.00159	0.00141	0.00124
3-4	16.50	12.8	2.11	481	0.00144	0.00130	0.00115	0.00101
4-5	18.50	13.2	2.44	543	0.00128	0.00115	0.00102	0.00089
5-6	20.70	13.9	2.88	624	0.00111	0.00100	0.00089	0.00078
6-7	23.40	14.8	3.46	734	0.00094	0.00085	0.00076	0.00066
				TEQ %	10%	69%	20%	1%

The dioxin exposure inputs for the model were based on those identified by Kreuzer et al.<sup>9</sup> for maternal and infant body burden at parturition and breast milk dioxin levels and feeding rate during nursing or during formula feeding. The daily TEQ dose was calculated based on an assumed concentration of 0.55 pg/g milk fat (this assumption was not varied for 50<sup>th</sup> and 95<sup>th</sup> percentile comparisons) with 70% depuration of breast milk concentrations over the six month feeding period. After six months of nursing, the infant is assumed to begin a pattern of age-specific intake of fruits, vegetables, grains, meats, eggs, dairy and fish at the 50<sup>th</sup> and 95<sup>th</sup> percentile rate as summarized by Williams et al.<sup>13</sup> and USEPA<sup>10</sup>. Table 2 summarizes the dioxin TEQ absorbed doses for each food category based on weighted mean estimates for North America as summarized by JECFA<sup>1</sup> and 50% bioavailability for all food types (except breast milk). Fruits and vegetables were assumed to have comparable weighted mean dioxin TEQ levels, and eggs were assumed to have comparable levels to that reported for meats. All of the TEQ doses were separated into congener-specific TEQ values based on the percentage distribution of congeners reported in > 600 human breast milk samples by Furst et al.<sup>14</sup>. Furst et al. showed that three congeners (TCDD, PeCDD and 2,3,4,7,8-PeCDF) account for nearly 80% of the total dioxin TEQ (WHO TEQ) in the breast milk fat. To simplify the calculations, congeners with the same WHO TEF value were combined (i.e., all hexaCDD/F and all heptaCDD/F congeners) and those with < 0.1% contribution to the total TEQ were omitted (OCDD, OCDF, and 1,2,4,7,8-PeCDF).

Environmental exposures to dioxins were assumed to occur via urban residential exposures, predominantly from incidental soil ingestion and dermal contact. Table 2 summarizes the 50<sup>th</sup> and 95<sup>th</sup> percentile values for average daily dose (ADD) corresponding to the child soil ingestion and child dermal contact doses in a probabilistic risk assessment for an urban residential setting (Paustenbach et al.<sup>15</sup>), assuming a soil dioxin TEQ of approximately 1 ppb. Dioxin bioavailability via soil ingestion was assumed to be 25%, and via dermal contact was 1.75%. Parameters for which probability density functions were utilized included residence duration, soil-to-skin adherence factor, child soil ingestion rate, body weight, and TCDD reference dose (assuming hazard index = 1.0). Point estimate values were used for exposure frequency (350 days/yr) and body part-specific skin surface area. A lognormal TCDD reference dose distribution with range from 1 to 20 pg/kg-day and mean of 8.67 pg/kg-day was utilized to develop the daily

environmental dose estimates (50<sup>th</sup> and 95<sup>th</sup> percentiles) corresponding to a uniform 1 ppb TEQ soil concentration in an urban residential setting.

**Table 2. Model Inputs for Daily TEQ Dose (pg/kg-day)**

	Dietary Dose		Soil Ingestion Dose		Dermal Dose	
Age (years)	50th Percentile	95th Percentile	50th Percentile	95th Percentile	50th Percentile	95 <sup>th</sup> Percentile
0.5-0.99	6.2	14.4	0.63	2.3	0.3	0.48
1-2.99	3.2	8.3	0.46	1.7	0.28	0.45
3-4.99	2.1	5.5	0.34	1.3	0.26	0.41
5-6.99	1.4	3.9	0.26	1.0	0.24	0.39

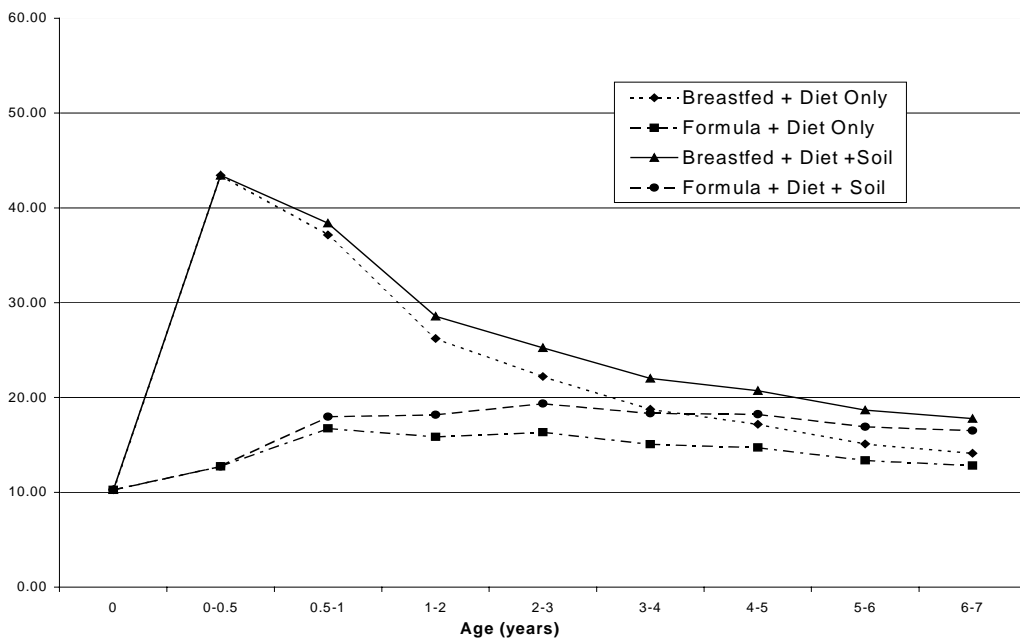
**Results and Discussion**

Figure 1 illustrates the outcome of the age-dependent half life model for children ages 0 to 7, including central tendency dietary and environmental exposures to dioxins (soil ingestion and dermal contact doses at the 50<sup>th</sup> percentile for 1 ppb dioxin TEQ levels in residential soils). These trends correspond to model inputs for absorbed daily TEQ doses of about 7 pg/kg-day for the 0.5 to 1 year period, and about 2 to 4 pg/kg-day through age 7 (50<sup>th</sup> percentile columns, Table 2). Lipid TEQ concentrations for children assumed to be breastfed for 6 months rose rapidly (4.5-fold in 6 months), then declined rapidly in the following 2 year period and continued to decline more slowly through age 7 (Figure 1). The infant assumed to be formula-fed for the first six months rose to a peak lipid TEQ level at 1 year, due to assumed high cow’s milk intake for the six months following exclusive formula feeding (also true for breastfed infant, but masked by the breast milk body burden). The lipid TEQ trends were essentially flat for the next 2 years, followed by a gradual decline through age 7. In both the breastfed and formula-fed examples, inclusion of absorbed TEQ burden (50<sup>th</sup> percentile) from soil ingestion and dermal contact with 1 ppb TEQ residential soils led to higher lipid TEQ levels (about 3 ppt or 12 to 14% higher on average over ages 0.5 to 7) but did not shift the general trends observed by modeling dietary contributions only. The total absorbed TEQ doses modeled in Figure 1 range from about 2 to 7 pg/kg-day, or about 2- to 7-fold higher than the tolerable daily intake values proposed by international groups<sup>1,2,3</sup>.

Figure 2 illustrates the outcome of the age-specific half life model for upper bound dietary (95<sup>th</sup> percentile intake rates) and environmental exposures to dioxins (soil ingestion and dermal contact doses at the 95<sup>th</sup> percentile for 1 ppb dioxin TEQ levels in residential soils). These trends correspond to absorbed daily TEQ doses of 17.2 pg/kg-day for the 0.5 to 1 year period, and about 5.3 to 10.5 pg/kg-day through age 7 (95<sup>th</sup> percentile columns, Table 2). Lipid TEQ concentrations for children assumed to be breastfed for 6 months rose rapidly (4.5-fold in 6 months), then continued to rise during the next six months (associated with assumed high intake of cow’s milk; Figure 2). After the first year, the breastfed child’s lipid TEQ levels declined slowly through age 7. The infant assumed to be formula-fed for the first six months showed rapidly rising lipid TEQ levels in the next six months followed by a secondary, more gradual rise in lipid TEQ levels that

peaked at about age 3 years, then gradually declined through age 7. In both the breastfed and formula-fed examples, inclusion of absorbed TEQ burden (95<sup>th</sup> percentile) from soil ingestion and dermal contact with 1 ppb TEQ residential soils led to higher lipid TEQ levels (about 9 ppt or 16 to 18% higher on average over ages 0.5 to 7) but did not shift the general trends observed by

Figure 1. Lipid TEQ (ppt) for Age-Dependent Half Life Model @ 50th Percentile

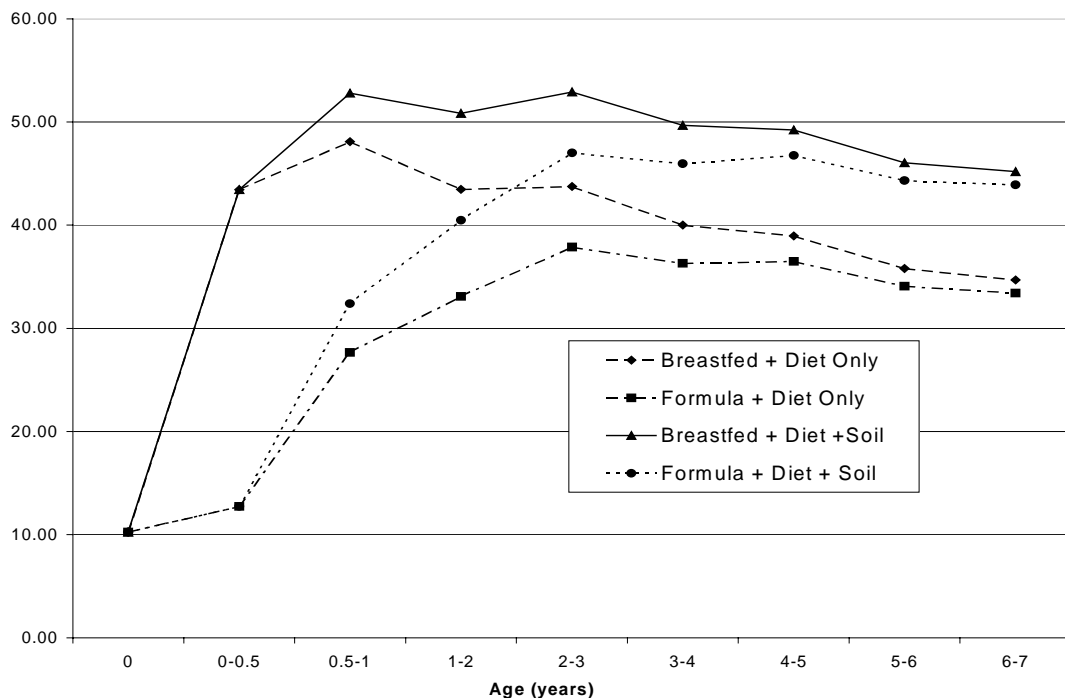


modeling dietary contributions only. Under the assumptions and parameters of our model, it appears that daily TEQ doses over 17 pg/kg-day in the 6 months after breastfeeding are necessary for the body burden trend to continue rising. This dose is some 5- to 17-fold higher than various tolerable daily intake estimates<sup>1,2,3</sup>.

While the modeled trends observed in Figure 2 correspond to a more substantial marginal influence of soil ingestion and dermal contact exposures, the observed trends are likely to be artifacts of forcing conservative assumptions into the age-dependent half life model. Perhaps most importantly, the modeled trends represented in Figure 1 are based on central tendency parameters and dose estimates. The artifactual trends are introduced in Figure 2 by presuming that 95<sup>th</sup> percentile dietary intake rates can occur in the absence of proportional increases in the child's growth rate, adipose volume, and body weight. The number of calories represented by the 95<sup>th</sup> percentile intake rates for carbohydrate-rich foods like dairy products, grains (cereals, bread), and eggs alone would correspond with above average growth rates; appropriate adjustment for caloric intake-related growth would result in corrected model trends that mimic Figure 1 more closely.

One must also consider that the 95<sup>th</sup> percentile TEQ dose estimates for soil ingestion and dermal contact are based on conservative risk assessment assumptions designed to avoid understating the reasonable maximum exposure and risk. There are considerable uncertainties associated with the combination of upper bound exposure parameters multiplied together to obtain the upper end of the probability distributions for soil ingestion and dermal contact average daily doses. Such doses are in fact not likely to represent sustained intake rates when averaged over the first six years of any

Figure 2. Lipid TEQ (ppt) for Age-Dependent Half Life Model @ 95th Percentile



given child's life. Despite these conservative choices and the relatively high assumed TEQ concentration (1 ppb) in residential soils, the age-dependent half-life model shows very modest changes in lipid TEQ levels from soil-related dioxin uptake and no remarkable change in the trends due to environmental (soil) exposures between ages 0.5 and 7 years.

This model takes the work of Kreuzer et al.<sup>9</sup> a bit further by incorporating congener-specific half life values for the dioxin congeners that comprise the vast majority of TEQ in human breast milk and adipose tissues. It also updates the dietary uptake estimates to those adopted through scientific consensus by JECFA<sup>1</sup>. With respect to half life values across congeners, we assumed that a 10% increase in half life occurs with each additional chlorine atom added to the 2,3,7,8-TCDD nucleus. The modeling of TEQ doses as if they behaved like TCDD (i.e., with its shorter half life) would lead to about an 11% underestimation of lipid TEQ concentrations in any body burden model. We recognize that such half life values are currently not known with certainty, and that other pharmacokinetic influences such as lower bioavailability of the higher chlorinated congeners (e.g.,

octa and hepta-chlorinated congeners) may also modify the results presented here. We ignored the octa-chlorinated congeners in our model because they contributed less than 0.1% of the human TEQ distribution; the hepta-chlorinated congeners were included in our model, but they also comprise a small proportion of the total TEQ in humans.

The age-dependent half life model for infants and young children (ages 0-7) corresponds to much lower body burdens than those estimated assuming a constant half life of 7 to 11 years for adults. For example, a steady state body burden in adults associated with absorbed daily doses equivalent to the upper bound tolerable daily intake of 4 pg TEQ/kg-day proposed by WHO<sup>2</sup>, assuming a 7.5 year half life, corresponds to a lipid TEQ level around 70 to 80 ppt TEQ. However, current body burden estimates for the general population of developed countries are generally less than 30 ppt TEQ, and appear to be continuing on a decreasing trend seen over the past two decades<sup>5</sup>. Insertion of a standard human half life assumption of 7.5 years into the infant and child body burden model leads to considerably higher peak lipid TEQ estimates, e.g., 150 to 200 ppt for the 50<sup>th</sup> percentile, and > 300 ppt for the 95<sup>th</sup> percentile (data not shown). Again, such estimates are confounded by the expected influence of growth on the steady state lipid concentration in infants and young children through age 7 years. They also tend not to agree with body burden measurements in younger individuals in developed countries with no unusual source of exposure<sup>9,16</sup>.

In conclusion, the age-dependent half life model applied to dioxin exposure in infants and children (ages 0-7), in conjunction with observed patterns of actual body burden TEQ measurements in children, suggest that the current tolerable daily intake estimates of 1 to 4 pg/kg-day are not likely to induce excessive body burdens in children. Due to the shorter effective half life values in children, these tolerable intake estimates based on correlation of adult body burdens to animal body burdens in reproductive toxicity studies probably overstate the body burdens and associated risks per daily dose in children.

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