# Infant Exposure to Dioxin-like Compounds in Breast Milk

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**We used a one-compartment, first-order pharmacokinetic model to predict the infant body burden of dioxin-like compounds that results from breast-feeding. Validation testing of the model showed a good match between predictions and measurements of dioxin toxic equivalents (TEQs) in breast-fed infants, and the exercise highlighted the importance of the assumption of the rate of dissipation of TEQs in the infant. We evaluated five nursing scenarios: no nursing (i.e., formula only), and nursing for 6 weeks, 6 months, 1 year, and 2 years. We assumed that an infant weighs 3.3 kg at birth and is exposed to a total of 800 pg TEQ/day by consumption of breast milk, leading to an estimated body weight-based dose of 242 pg TEQ/kg-day, which drops to 18 pg TEQ/kg-day after 1 year. This decline is due to declines in dioxin concentration in mother's milk and infant body weight increases. This range is significantly higher, on a body-weight basis, than adult TEQ exposure, which has been estimated to average about 1 pg TEQ/kg-day. For the nursing scenarios of ≥ 6 months, we predict that body burdens (expressed as a body lipid concentration) peak at around 9 weeks at 44 ppt TEQ lipid. We predict that the body burden of the formula-fed infants will remain below 10 ppt TEQ lipid during the first year. These results compare to the current adult average body burden of 25 ppt TEQ lipid. We also found that an infant who had been breast-fed for 1 year had an accumulated dose 6 times higher than a 1-year-old infant who had not been breast-fed. For a 70-year lifetime, individuals who had been breast-fed had an accumulated dose 3–18% higher than individuals who had not been breast-fed. *Key words:* breast milk, dioxin-like compounds, dioxins, furans, infant exposure, pharmacokinetic modeling. *Environ Health Perspect* 110:A325–A332 (2002). [Online 13 May 2002]**
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Several researchers have shown that infant exposure to dioxin-like compounds can be significant by the breast milk pathway (*1–4*). Ayotte et al. (*1*) used data on the concentrations of dioxin-like compounds [including dioxin and furan congeners as well as the dioxin-like polychlorinated biphenyls (PCBs)] in breast milk of Inuit populations in Nunavik (the Arctic region of Quebec, Canada) with a median concentration of 48 pg dioxin toxic equivalents (TEQ)/g lipid, to calculate an infant dose of 226 pg TEQ/kg-day. They applied a pharmacokinetic (PK) model to evaluate the impact of breast-feeding of dioxin TEQs on infant body burdens and on lifetime (up to 75 years) body burdens of TEQs. By studying the accumulation of dioxin-like compounds in humans over time, Patandin et al. (*2*) showed that 6 months of breast-feeding during the first 25 years of life could contribute 12% of the total dose of these compounds during those 25 years for men and 14% for women. Kreuzer et al. (*3*) and Lakind et al. (*4*) combined estimates of 2,3,7,8-tetrachlodibenzo-*p*-dioxin (TCDD) dose received by the infant via breast-feeding with PK models to demonstrate the initial significant elevation in infant body burdens of TCDD as a result of this exposure. Their models predicted that initially high body burdens declined as a result of infant body weight increases, depuration of residues, and reduced doses due to declines of residues of TCDD in mother's milk.

In this paper, we build on the efforts of other researchers (*1–4*) to model the impacts of breast-feeding on body burdens of dioxin-like compounds. We express body burdens in terms of picograms of dioxin TEQs per gram body lipid or parts per trillion TEQ lipid; these compounds are known to accumulate in lipid, and TEQ concentrations in mother's milk, blood, and other organs are often expressed on a lipid basis.

In this paper we focus on dioxin-like compounds expressed as a dose or concentration of dioxin TEQs. The TEQ concentration is the sum of the concentrations of the individual dioxin-like compounds multiplied by their respective toxicity equivalency factors (TEFs). The TEF scheme we used is the one promoted by the World Health Organization in 1998 (*5*). We use TEQ to signify the 29 compounds assumed to have dioxin-like toxicity, including the 7 polychlorinated dibenzo-*p*-dioxin (PCDD) and 10 dibenzofuran (PCDF) congeners, as well as the 12 dioxin-like coplanar PCBs, unless otherwise stated. We treat TEQs as a single compound. Even with the principal uncertainty of this approach, the limited validation and general comparison of modeled results with the measured values suggest that this may be a reasonable approach for evaluating trends in exposure to dioxin-like compounds via breast-feeding.

In this paper we describe and validate a simple pharmacokinetic model for evaluating the impact of breast-feeding on infant body burdens. We then apply the model to five scenarios: formula only, and nursing times of 6 weeks, 6 months, 1 year, and 2 years. We also performed another sensitivity analysis test that doubled the dose received by the infant and also doubled the infant's initial body burden at birth to determine how these parameters affect model predictions.

## Modeling the Impact of Breast-Feeding on Infant Body Burden

To better evaluate the impact of nursing on infants, we used a one-compartment non-steady state PK model to predict dioxin tissue levels in infants. The PK model is based on the following differential equation describing the mass balance of dioxin in lipids (*6*):

$$\partial a(t)/\partial t = abs\ D(t) - k(t)a(t) \qquad [1]$$

$$c(t) = a(t)/[1{,}000\ V(t)], \qquad [2]$$

where $a(t)$ is the total mass of dioxins in lipid (picograms) at time $t$; $t$ is time (days); $abs$ is the fraction of ingested dose that is absorbed into the lipid compartment (unitless); $D(t)$ is the ingested dose of TEQs (picograms per day) at time $t$, $k(t)$ is the elimination rate function (per day) at time $t$; $c(t)$ is the concentration of dioxins in lipid (picograms per gram) at time $t$; and $V(t)$ is the lipid weight (kilograms) at time $t$.

This modeling framework, as well as the parameter assignments we used in this study, derive heavily from the efforts of Lakind et al. (*4*) and Kreuzer et al. (*3*). Lakind et al. (*4*) also used a first-order, single compartment model to predict the accumulation of TCDD and dichlorodiphenyldichloroethane (DDE) in infants from breast-feeding. Lakind reviewed the literature to assign critical model parameters that are also required in our study, such as the absorption of ingested

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dose. Lakind et al. (*4*) assumed a 95% absorption of TCDD, whereas the literature that we reviewed for this work suggests a lower absorption for TEQ intakes (80%). Lakind et al. (*4*) also reviewed the literature to develop a model of declining concentrations in mother's milk. We used the same justification in this study to consider this decline. A key input to the Lakind model (*4*), as in our model, is a first-order rate of elimination; Lakind et al. (*4*) used an elimination rate derived by Kreuzer et al. (*3*). The Lakind model, like our model, does not model any specific process of TCDD elimination; it simply requires assignment of a first-order elimination rate. Kreuzer et al.'s model (*3*) was slightly more complex and more physiologically based than the model of Lakind et al. (*4*) and the one we used in this study. Specifically, ingested TCDD is deposited into body adipose tissue, from which it partitions into richly perfused tissue (a single compartment composed of brain, kidney, intestines, liver, and spleen) and instantaneously into muscle tissue. Elimination of TCDD is modeled as the sum of metabolic (breakdown) and nonmetabolic (fecal elimination) pathways. We estimated fecal elimination as the product of the lipid tissue concentration and the mass of lipids excreted over time. Using physiologic data on the mass of lipids in fecal samples that varied with age, Kreuzer et al. (*3*) found that the overall half-life of TCDD in infants was driven by fecal elimination. This overall half-life was on the order of weeks at infancy, and it increased through infancy until the metabolic pathway dominated in adulthood. The overall half-life of TCDD in adults was more on the order of years rather than weeks.

One key assumption of this simplistic framework is that dioxins are instantaneously distributed to all body lipids. This is a common assumption for TCDD PK modeling in humans, adopted in multicompartment (*7*) and single-compartment (*3,4,8*) models. The model of Carrier et al. (*9,10*) alternately has a nonlinear response to doses, with different partitioning to the liver and other body lipids as a function of body concentration: when the overall body concentration is high, more of the dioxin dose is partitioned to the liver, whereas at lower body concentrations, the partitioning to the liver is lower.

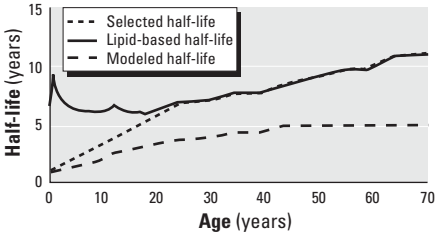


**Figure 1.** Comparison of the selected half-life of TEQs in the body with lipid-based half-life (*6*) and modeled half-life (*3*) for TCDD.

The other key assumption in our model is that a dioxin TEQ dose behaves as a single compound in humans and is described by a single dissipation half-life. Ayotte et al. (*1*) modeled TEQ body burdens from infancy to adulthood, but it was unclear whether they modeled individual congeners or TEQs as one compound. Campbell et al. (*8*) used a framework similar to the one we used and modeled individual congeners for an industrial exposure study.

An elimination rate function, $k(t)$, for TCDD has been modeled as a function of the percent body fat, $k$(fat) (*6,11,12*). This empirical function, $k$(fat), was curve-fit from data on Vietnam veterans (*11*) who had approximately 25% body fat. As the percentage of body fat increases, the elimination rate is modeled to decrease (equivalently, the half-life is modeled to increase) significantly. Given a range of body fat over a lifetime, from a low of 15% (teenage years) to a high of over 40% (elderly females), these relationships suggest a half-life of TCDD ranging from approximately 6 years to > 20 years, with a general trend toward an increase in half-life as individuals age (because the percentage of body fat increases with age).

None of these efforts, however, identified processes or factors critical for infants. With a body fat of around 15% at birth, the half-life of TCDD is approximately 6 years using these $k$(fat) relationships. Kreuzer et al. (*3*), however, developed a procedure for modeling the overall elimination half-life for TCDD in infants that considers metabolic ($t_m$; breakdown by enzymes) and nonmetabolic ($t_f$; fecal elimination) processes. Other key parameters included total body lipid mass and liver volumes, which change over time, and a reference half-life for an adult. For their "reference adult" at 40 years of age, Kreuzer et al. (*3*) cited an overall half-life of 5 years, based on information from Geyer et al. (*13*). The Kreuzer et al. (*3*) model showed a rise in half-lives from a low of < 0.5 years at birth to a high of 5 years at an adult body fat mass of 20 kg. Thus, the model of Kreuzer et al. (*3*) is different than the $k$(fat) models (*6,11,12*): the model of Kreuzer et al. (*3*) predicts half-lives that never exceed 5 years, whereas the other approaches predict half-lives that never go below 6 years.

For purposes of this assessment, we assumed that the overall half-life for the early years of life more closely follows the trend as derived in the modeling exercises by Kreuzer et al. (*3*). For later years, we believe that the $k$(fat) model is more valid. Therefore, for this study, we adopted a hybrid of these assumptions, as shown in Figure 1; point estimates of the half-life [the model parameter, $k(t)$, equal to 0.693/half-life] are shown in Table 1. The half-life at birth starts at the low value of 0.4 years and then slowly rises to the levels predicted by the $k$(fat) models by approximately 25 years of age. The half-life assumptions remain an obvious uncertainty for this type of modeling approach. Not only is there a disparity in the literature with regard to this critical assumption, but the literature was only specific to TCDD, not TEQs.

Using the estimated dioxin concentration in breast milk, the dose to the infant was modeled as follows:

$$D(t) = C(t)\, f\, IR, \qquad [3]$$

**Table 1.** Parameters used for modeling the impact of breast-feeding on body burden and lipid concentrations of TEQs from infancy to adulthood.

| | PK modeling parameters | | | Dioxin TEQ dose (pg/day) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Breast-fed | | | |
| Age | BW (kg) | Lipid[a] | Half-life (years)[b] | Formula | 6 weeks | 6 Months | 1 Year | 2 Years |
| Birth | 3.3 | 0.14 | 0.40 | 54 | 800 | 800 | 800 | 800 |
| 1 Month | 4.3 | 0.16 | 0.50 | 54 | 733 | 733 | 733 | 733 |
| 2 Months | 4.6 | 0.18 | 0.60 | 54 | 667/54 | 667 | 667 | 667 |
| 3 Months | 6.0 | 0.20 | 0.70 | 54 | 54 | 600 | 600 | 600 |
| 4 Months | 6.7 | 0.22 | 0.75 | 54 | 54 | 533 | 533 | 533 |
| 5 Months | 7.4 | 0.23 | 0.80 | 54 | 54 | 467 | 467 | 467 |
| 6 Months | 7.9 | 0.25 | 1.00 | 54 | 54 | 400 | 400 | 400 |
| 7 Months | 8.4 | 0.25 | 1.00 | 54 | 54 | 54 | 367 | 367 |
| 8 Months | 8.8 | 0.24 | 1.05 | 54 | 54 | 54 | 333 | 333 |
| 9 Months | 9.2 | 0.24 | 1.08 | 54 | 54 | 54 | 300 | 300 |
| 10 Months | 9.4 | 0.23 | 1.10 | 54 | 54 | 54 | 267 | 267 |
| 11 Months | 9.8 | 0.23 | 1.12 | 54 | 54 | 54 | 233 | 233 |
| 1 Year | 11.3 | 0.23 | 1.14 | 54 | 54 | 54 | 200 | 200 |
| 2 Years | 13.3 | 0.20 | 1.39 | 54 | 54 | 54 | 54 | 200 |
| 5 Years | 19.7 | 0.15 | 2.12 | 59 | 59 | 59 | 59 | 59 |
| 11 Years | 41.1 | 0.15 | 3.60 | 64 | 64 | 64 | 64 | 64 |
| 18 Years | 65.1 | 0.13 | 5.33 | 65 | 65 | 65 | 65 | 65 |
| 34 Years | 71.5 | 0.21 | 7.70 | 65 | 65 | 65 | 65 | 65 |
| 55 Years | 73.8 | 0.27 | 9.76 | 65 | 65 | 65 | 65 | 65 |

BW, body weight.
[a]Fraction of body weight that is lipid. [b]Half-life of dioxin residues in body.

where $D(t)$ is the ingested dose of TEQs (picograms per day) at time $t$, $C(t)$ is the concentration in milk fat (picograms per gram), $f$ is the fraction of fat in breast milk, $IR$ is the ingestion rate of breast milk (kilograms per day), and $t$ is time. The dose term, $D(t)$, can easily be converted to a body weight-based dose term by dividing by infant body weight. The milk fat concentration and the infant body weight were modeled to vary over time; we assumed that the rate of ingestion of mother's milk and the fraction of fat in the mother's milk were constant over the duration of breast-feeding.

Smith (*14*) reported that studies in Great Britain and Houston, Texas, found that the breast milk ingestion rate for 7- to 8-month-old infants ranged from 677 to 922 mL/day and 723 to 751 mL/day, respectively, and that breast milk ingestion rates remain relatively constant over an infant's life. Smith (*14*) also assumed that mother's milk has a 4% fat content and that 80% of the ingested dioxins in mother's milk are absorbed. We adopted these assumptions for the modeling exercise described in this paper: $abs$ = 0.80, $IR$ = 0.8 kg/day (which assumes 1 L milk weighs 1 kg), and $f$ = 0.04. Lakind et al. (*4*) reviewed additional literature to support a selection of 95% for absorption of TCDD from breast milk ingestion. However, there is evidence that the absorption is lower as the degree of chlorination increases, particularly for the highest chlorinated congener, octachlorodibenzo-*p*-dioxin (OCDD), with an absorption measured to be between 2% and 15% (*15*). Because TEQ doses are dominated by the lower chlorinated congeners, the low absorption of higher chlorinated congeners may be less critical, justifying the selection of 0.80 for $abs$ for TEQ doses.

The lipid weight of the individual, $V(t)$, was calculated as the product of the fraction of body lipid and the full body weight of the individual. A typical infant (average of male and female) weighs about 3.3 kg at birth, 7.9 kg at 6 months, and 11.3 kg at 1 year of age (*16,17*). For dose calculation and PK modeling in this study, we averaged monthly average weights for males and females for the first 12 months of life and then for later years into adulthood (*16*). The body lipid fraction is about 0.15 at birth. It then increases to > 0.20 within 6 months, decreases into childhood, and increases again through adulthood to > 0.30 after 60 years of age (*17*). Point estimates of full body weight and lipid fraction as a function of age are shown in Table 1.

The last parameter for the model is the initial body burden in infants at birth. We assumed that this initial body burden is 10 ppt TEQ lipid, reasonably similar to the 11.9 ppt TEQ lipid found in stillborn adipose tissue by Kreuzer et al. (*3*), although their TEQ concentration included only dioxin and furan congeners.

## Impact of Breast-Feeding on Infant Body Burden and a Limited Model Validation

Kreuzer et al. (*3*) presented data on adipose tissue and liver from 3 stillborn infants and 17 infants who had died from sudden infant death syndrome (SIDS). Nine of the 17 infants had been breast-fed for some portion of their lives, whereas the other 8 infants were formula-fed. Average congener and TEQ adipose tissue concentrations for these three groups are shown in Table 2. The highest TEQ concentrations were found in the infants who had been breast-fed, with lipid concentrations of 15.9 ppt TEQ (PCDD/PCDF only), compared to formula-fed infants who had concentrations of 4.3 ppt TEQ lipid. All congener concentrations in breast-fed infants were higher than those for formula-fed infants. The concentrations from breast-fed infants included 4 infants who were weaned several weeks before their deaths from SIDS. This may have generally led to reductions in their body burdens because their higher daily intake from breast-feeding was reduced after weaning. The average TEQ concentration for the 5 infants who died while still breast-feeding was 20.1 ppt TEQ lipid. The highest concentration found, 35 ppt TEQ lipid, was for the infant who was breast-fed the longest (19 weeks) and who died at that time. Other breast-fed infants, however, did not have as much impact: infants who died at 12 and 16 weeks, while still breast-feeding, had concentrations of 9 and 7.5 ppt TEQ lipid, respectively. Kreuzer et al. (*3*) concluded that breast-fed infants had elevated TEQ concentrations compared to formula-fed infants; they also observed that breast-fed infants had lipid TEQ concentrations that were within the range or lower than the values published for adults.

**Table 2.** Average adipose tissue concentrations of dioxins and furans in stillborn, formula-fed, and breast-fed infants (pg/g lipid).

| Compound | Stillborn ($n$ = 3) | Formula-fed ($n$ = 8) | Breast-fed ($n$ = 9) |
|---|---|---|---|
| TCDD | 1.6 | 0.4 | 1.7 |
| 1,2,3,7,8-PentaCDD | 3.4 | 1.1 | 4.9 |
| 1,2,3,4,7,8-HexaCDD | 2.5 | 1.0 | 4.0 |
| 1,2,3,6,7,8-HexaCDD | 8.8 | 4.0 | 19.9 |
| 1,2,3,7,8,9-HexaCDD | 1.3 | 0.7 | 3.7 |
| 1,2,3,4,6,7,8-HeptaCDD | 12.9 | 5.0 | 25.2 |
| OCDD | 51.2 | 29.1 | 91.6 |
| 2,3,7,8-TCDF | 1.4 | 1.9 | 1.1 |
| 1,2,3,7,8,-PentaCDF | 0.2 | 1.0 | 0.5 |
| 2,3,4,7,8-PentaCDF | 9.2 | 3.1 | 10.6 |
| 1,2,3,4,7,8-HexaCDF | 3.7 | 1.7 | 3.5 |
| 1,2,3,6,7,8-HexaCDF | 2.4 | 1.0 | 2.8 |
| 2,3,4,6,7,8-HexaCDF | 1.0 | 0.2 | 1.1 |
| 1,2,3,7,8,9-HexaCDF | 0.1 | 0.1 | 0.1 |
| 1,2,3,4,6,7,8-HeptaCDF | 3.6 | 1.6 | 3.8 |
| 1,2,3,4,7,8,9-HeptaCDF | 0.4 | 0.1 | 0.1 |
| OCDF | 2.1 | 1.8 | 1.6 |
| TEQ | 11.9 | 4.3 | 15.9 |

Data from Kreuzer et al. (*3*). Average congener concentrations were calculated by assuming that nondetects equal one-half the detection limit.

Abraham et al. (*18*) reported a study in Germany in which blood samples from 80 breast-fed infants between 4 and 11 months of age were sampled for 17 dioxin-like PCDD/PCDFs. Of these 80 infants, 27 were from a region where a copper recycling plant led to elevations in the mother's milk. The TEQ blood concentration in this group of 80 children at 11 months of age ranged between 2 and 107 ppt lipid, with a median of 25.3 ppt; these TEQs were based only on PCDD/PCDF and were calculated using the older international toxicity equivalency scheme (*18*). Of these children, 6 had TEQ concentrations > 50 ppt lipid, and 5 of these 6 were from the region affected by the copper recycling plant. From a control group of 21 children who had been formula-fed, individual dioxin measurements were performed in 5 children. Concentrations ranged from 1.9 to 3.2 ppt TEQ lipid at 11 months of age.

Patandin et al. (*19*) studied the plasma levels of 4 PCBs in 173 Dutch children who were 3.5 years of age, 91 of whom had been breast-fed and 82 formula-fed. Children in the breast-fed group had significantly higher median PCB levels in plasma ($p < 0.0001$) than children in the formula-fed group. The four PCBs measured by Patandin et al. (*19*) were PCBs 118, 138, 153, and 180. The median sums of these four PCBs in the two groups of children were 0.75 µg/L in the breast-fed group versus 0.21 µg/L in the formula-fed group. By means of an extensive questionnaire on dietary history combined with data on concentrations of dioxin and

PCBs in food provided by the Dutch National Institute of Public Health and the Environment, they were able to determine that the TEQ intake via diet was virtually indistinguishable in the two groups. They found that PCB levels in the breast-fed children were significantly correlated with the period of breast-feeding ($r$ = 0.63), milk PCB levels ($r$ = 0.39), and the total TEQ in breast milk ($r$ = 0.36). Patandin et al. (*19*) concluded that PCB levels in Dutch children are the result of exposure through breast milk and *in utero* exposure and that the influence of dietary intake of PCBs after weaning is small compared to the intake during breast-feeding.

Abraham et al. (*20,21*) sampled blood from formula-fed and breast-fed infants for dioxins, furans, and PCBs. Results showed that the body burden of dioxin-like compounds was more than an order of magnitude higher for the breast-fed infants than the formula-fed infants during both time periods. PCDD/PCDF TEQ concentrations ranged from 34.7 ppt lipid (11 months) to 43.9 ppt lipid (25 months) in breast-fed infants compared to 2.7–3.3 ppt TEQ lipid for the formula-fed infants. Dioxin-like PCB concentrations were also an order of magnitude different, with the breast-fed infants having a concentration of 31.4 ppt TEQ lipid compared to 2.5 ppt TEQ lipid for the formula-fed infants at 11 months. (PCB 126 was not measured at 25 months, so a comparison for that age is not informative.) The increase in the lipid-based PCDD/PCDF TEQ concentration in the blood of the 25-month-old breast-fed infants was attributed to the relative decrease in body fat mass during the period between sampling and slight increases in body burden concentrations.

These studies demonstrate the impact of breast-feeding, but they do not contain the type of information needed for model validation. For the data to be appropriate for model validation, breast milk concentrations should be taken at the same time infant body burden measurements are taken. The breast milk concentrations are used to provide the "independent" model driving term (the dose term), and the body burden measurements provide the "dependent" model prediction (the infant body lipid concentration).

One study included this type of data. Abraham et al. (*22*) studied PCDD/PCDF/PCB levels in blood of six breast-fed infants and breast milk from the infants' mothers. A portion of this data was reported in their earlier articles (*20,21*). In our analysis, we focus on the PCDD/PCDF TEQ concentrations reported in Abraham et al. (*22*) because PCB concentrations were not uniformly available for mother's milk and infant blood for all six mother/child pairs.

Two of the infants were the second children from mothers whose first child was also tracked by Abraham and colleagues (*20,21*). For these two second children, both the mothers' milk and the infants' body burdens were significantly lower; specifically, the comparison of first and second children, respectively, were 34.7 ppt TEQ lipid compared to 11.9 ppt TEQ, and 44.2 ppt TEQ compared to 18.8 ppt TEQ. The comparison of the mothers' milk from the first to second children was similarly disparate: the first mother had concentrations ranging from 14 to 24 ppt TEQ lipid for the first child, but 13 to 14 ppt TEQ lipid for the second child. The other mother showed a range of 15–27 ppt TEQ lipid for the first child, but 13–18 ppt TEQ lipid for the second child. Apparently, breast-feeding of the first child resulted in higher body burdens for this infant compared to the second infant and a lower body burden for the mother when the second infant was born.

Table 3 shows the results of the model validation excercise based on data reported by Abraham et al. (*22*). Abraham et al. (*22*) measured concentrations in breast-milk two times for 5 of 6 children. The one child whose mother had only one measurement was breast-fed for only 7 weeks; all other children were breast-fed for 26–32 weeks. We linearly extrapolated concentrations within the breast-feeding period from the two available data points. For example, for the first mother/child pair listed in Table 3, the mother's milk was analyzed during month 2 and month 11 after the child's birth; TEQ concentrations were 23.5 and 14.0 ppt TEQ lipid, respectively. We extrapolated these concentrations backward to give an estimated concentration of 24.6 ppt TEQ at birth. Likewise, forward extrapolation gave an estimated TEQ concentration of 22.4 ppt TEQ for month 3, assuming linear decline. The infant body burden was determined by blood measurements at approximately 1 year of age for each child. Abraham et al. (*22*) also provided the amount of time of full breast-feeding (Table 3).

For modeling the infant body burden, we assumed that the *IR* for mother's milk is 800 mL/day. After weaning, we assumed that the infant's dose was 54 pg TEQ/day. This is the dose developed for the age range of 1–5 years by the U.S. EPA (*23*). Little information is available on the dioxin content of baby formula and baby food; therefore, it is not known whether the dioxin dose consumed by infants in formula or other foods after weaning may be higher or lower than the assumed 54 pg/TEQ/day.

The rate of dissipation of dioxin residues is a principal uncertainty for this model. Two possibilities include the rapid dissipation (half-life < 1 year) of TCDD residues in infants (*3,4*) and the much longer half-life of around 7 years, based on a model of half-life as a function of body fat (*6,11,12*). This model validation exercise tested the appropriateness of the lower half-life approach adopted in this model, as shown in Figure 1, against an assumption of a constant 7-year half-life for TEQs during the first year of life.

As shown in Table 3, the model predictions at the selected dissipation rate (half-life < 1 year) were significantly nearer to observations than the predictions with the longer half-life. The average predicted concentration for the rapid dissipation rate for the six infants was 26 ppt TEQ lipid compared to the average observed concentration of 23.5 ppt TEQ lipid. With a 7-year half-life, the predicted concentrations were all higher, with an average of 39 ppt TEQ lipid. The model, applied with the shorter half-life, also seemed adequately responsive to lower or higher exposures in infants. For the infant who was breast-fed for only 7 weeks with a low concentration in the mother's milk, the blood concentrations were 5.0 ppt TEQ lipid at 13 months of age compared to a predicted 10 ppt TEQ lipid. The infant who was exposed to the highest dioxin concentration in breast milk had the highest body burden measurement (44.2 ppt TEQ lipid) and also the highest predicted concentration (36 ppt TEQ lipid).

**Table 3.** Model validation data and results (pg TEQ/g lipid).

| | Observed data[a] | | | | Model predictions, child TEQ C[b] | |
|---|---|---|---|---|---|---|
| | Milk TEQ[c] | | | | Selected HL | Long HL |
| Description | 1st | 2nd | Child TEQ[b] | Weeks BF[d] | < 1 year[e] | 7 years[f] |
| Mother 1, 1st child | 23.5 (2) | 14.0 (11) | 34.7 (11) | 26 | 34 | 51 |
| Mother 1, 2nd child | 13.7 (2) | 12.7 (5) | 11.9 (11) | 29 | 27 | 39 |
| Mother 2, 1st child | 26.5 (2) | 15.2 (11) | 44.2 (12) | 30 | 36 | 56 |
| Mother 2, 2nd child | 18.3 (2) | 13.1 (6) | 18.8 (12) | 32 | 27 | 41 |
| Mother 3, only child | 13.7 (2) | NA | 5.0 (13) | 7 | 10 | 16 |
| Mother 4, only child | 12.7 (2) | 13.0 (6) | 26.5 (12) | 30 | 21 | 32 |
| Average C (pg/g TEQ) | | | | 23.5 | 26 | 39 |

Abbreviations: BF, breast-fed; C, concentration. Values in parentheses indicate the month after birth when sampling was performed.
[a]Data from Abraham et al. (*22*). [b]Concentration of TEQ in blood of infants. [c]Breast milk TEQ concentration. [d]Weeks of full breast-feeding. [e]Half-life model selected for model validation and further analysis. [f]Alternate half-life model in which half-life was 7 years at birth.

Even with the key uncertainties identified above, including the use of a simple, one-compartment PK model and the modeling of dioxin TEQs as though TEQ were a single compound, this approach appears to predict infant TEQ body burdens within the range observed and is adequately responsive to the different conditions of high and low exposure via breast-feeding.

This model validation exercise demonstrated the importance of half-life to predictions of infant TEQ body burden concentrations and the apparent validity of the short half-life for infants in contrast to the half-life on the order of years that appears to be valid for adults. At least in the context of this simple model, it would not be appropriate to assign half-lives on the order of years for infant body burden modeling. Besides this half-life, model predictions of infant body burden are most impacted by the dose of TEQs infants receive through breast milk or otherwise. The model responds linearly to changes in dose—if the dose taken in by the infant doubles, the infant body burden predictions double. Obviously, the initial concentration of TEQs in the infant is also affected by the mother's body burden. The remaining parameters are the infant physiologic parameters determining the size of the lipid reservoir into which the ingested dioxins deposit, the changing infant body weight and lipid fraction. The model responds in an inverse linear manner to these parameters—if the reservoir size is halved, the concentration doubles. There is realistically not a large range for these parameters and the average values selected below are probably sufficient for most assessment needs.

The dose is simply a picogram TEQ per day quantity taken in by the infant, which is determined externally; the model requires only the picogram TEQ per day input. It is a function of the amount of milk a child drinks, the lipid content of the mother's milk, the TEQ concentration in the milk, the fraction of ingested dioxin that is absorbed, and any other assumptions the user may make regarding the decline or rise in mother's milk concentration (or changes to lipid content of the milk) over time. We conducted several model runs to evaluate different nursing scenarios. We selected midrange values for all of the dose model parameters; only the time of nursing varied. We expected that this exercise would reasonably bound the exposures the majority infants in the United States would receive. Some mothers could have high TEQ body burdens because of an unusual or occupational exposure. To evaluate this possibility, we conducted a sensitivity test to evaluate the effect of doubling the mother's body burden, which resulted in not only a doubling of dose but also influenced the initial concentrations of TEQs in the infant.

## Scenario Development and Evaluation

We used this modeling framework to evaluate five breast-feeding scenarios: formula-feeding only or breast-feeding for 6 weeks, 6 months, 1 year, or 2 years. These scenarios encompass current trends. In a comprehensive documentation of statistics for children born between 1990 and 1993, the Centers for Disease Control and Prevention (*24*) reported that 55% of all babies breast-fed, with about one-half breast-feeding longer than 5 months. The average duration of breast-feeding was 28.7 weeks. In a policy statement, the American Academy of Pediatrics (*25*) stated that exclusive breast-feeding is ideal nutrition and is sufficient to support optimal growth and development for 6 months after birth. They recommend that breast-feeding continue for at least 12 months, and thereafter for as long as mutually desired.

To model these scenarios, it was important to assign values to the mother's milk concentration regime over the breast-feeding period. This regime includes the assignment of an initial concentration and a scheme to model the expected decline over time. We assumed that the dioxin concentration in breast milk is 25 ppt TEQ lipid when lactation begins. This is the current average adult tissue concentration derived in the U.S. EPA's draft dioxin reassessment (*23*) from recent studies of dioxins in blood in background settings of the United States. By adopting this concentration as the initial concentration in breast milk, we assume that lipid concentrations of TEQs are equal in different lipid reservoirs and that a lipid-based blood concentration is equal to the lipid-based breast milk concentration, an assumption that is reasonably well recognized in the literature (*23*).

More importantly, however, the 25 ppt TEQ initial concentration in mother's milk can also be characterized as conservative because it is higher than is currently likely for the average U.S. woman of child-bearing age. The average adult concentration of 25 ppt TEQ lipid includes younger and older adults. It has been well established in the literature that dioxin exposures were higher during the middle decades of the 20th century than they are now (*6,23,26*) and that body burdens in older individuals are currently significantly higher than in younger individuals. It is likely that women of child-bearing age in the United States now have average body burdens < 25 ppt TEQ lipid, probably < 20 ppt TEQ lipid. However, it is also likely that there are populations with concentrations higher than this overall average. For example, concentrations of dioxin-like compounds in the blood of sport fishers and nonfishers in the Great Lakes region were higher, on average, than 25 ppt TEQ, and higher concentrations were found in sport fishers as compared to nonfishers (*27–29*).

The concentration of dioxin in breast milk is expected to change because lactation provides a significant avenue of depuration. Therefore, the scenarios require an assumption of the decline from the initial breast milk concentration of 25 ppt TEQ lipid. Lakind et al. (*4*) cited several references in which measurements of breast milk concentrations of lipophilic compounds (PCBs, DDE, DDT, PCDDs/PCDFs) were shown to decline during the course of lactation. They fit available data on TCDD to a curve, and their resulting relationship showed an 86% loss over 6 months. This is comparable to a modeling effort by Kreuzer et al. (*3*), who modeled a 70% decline in TCDD concentrations after 6 months. Their model was more mechanistic than that of LaKind et al. (*4*) and added the loss by breast milk to an overall female body burden model, which included inputs by food consumption and outputs by metabolic and nonmetabolic pathways. Patandin et al. (*2*), in their modeling of dioxin exposures from infancy to adulthood, cited data from Germany and England and concluded that breast milk concentrations of TCDD decline by 20% every 3 months. The data described in reports by Abraham et al. (*24–26*) suggested a TEQ decline of approximately 40% from early lactation to just under 1 year of breast-feeding.

Based on this information, we assumed that the initial 25 ppt TEQ lipid concentration in breast milk decreased linearly by 50% after 6 months, with a 50% decrease by the end of 12 months, and a total decline of 75% from initial concentrations. These concentration declines are in the middle of the range reported above. They translate to concentrations of 12.5 ppt TEQ lipid after 6 months and 6.3 ppt TEQ lipid after 1 year. For the 2-year breast-feeding scenario, we assumed that concentrations in breast milk remain at 6.3 ppt TEQ lipid from the end of the first until the end of the second year.

Table 1 shows key parameters for the dose calculation and for PK modeling for months during the first year of life and for key years thereafter. The dose parameters include infant body weights as well as doses of dioxin TEQ expressed in terms of picograms per day by either breast-feeding or background exposures. Breast-feeding doses drop from 800 pg TEQ/day (242 pg TEQ/kg-day on a body-weight basis) at birth to 200 pg TEQ/day (18 pg TEQ/kg-day) at 1 year. We assumed that the concentration in breast milk remains constant at 6.3 ppt TEQ lipid (dose to infant of 200 pg TEQ/day) from year 1 to year 2 during breast-feeding

for the 2-year nursing scenario. We assumed that the dose after breast-feeding equals background doses; the U.S. EPA (*27*) determined the background dose to be 54 pg TEQ/day (for ages 1–5 years), 59 pg/day (6–11 years of age), 64 pg TEQ/day (12–19 years of age), and 65 pg TEQ/day (> 19 years of age).

We used ModelMaker, Version 4.0 (ModelKinetix.com, Oxford, UK) to run the model and generate graphic results. We used Runge-Kutte numerical integration methods with a specified number of steps equaling 10,000 over a 70-year simulation (about 2.5 days/step).

The results from this exercise show the body burdens, expressed as body lipid concentrations, from birth up to 70 years of age (Figure 2) and then for a narrower time frame, from birth to 10 years of age (Figure 3). Other results for these five scenarios are shown in Table 4, including peak concentrations in the infant, time when the peak occurred, the area under the curve (AUC) corresponding to different times, and the ratio of the AUC for the breast-feeding scenarios and the AUC for formula feeding only. The AUC is defined as

$$\mathrm{AUC}(t) = \Sigma\, c(t), \qquad [4]$$

where AUC($t$) is the area under the curve (parts per trillion-day) at time $t$ and $c(t)$ is the lipid-based concentration in the infant each day (parts per trillion TEQ lipid). The AUC is a measure of accumulated exposure. For example, 1 year at a lipid-based concentration of 10 ppt would yield an AUC of 3,650 ppt-day (10 ppt × 365 days). A lifetime at an average body lipid concentration of 10 ppt would yield an AUC of 255,500 ppt-day (10 ppt × 70 years × 365 days/year). The AUC provides a parameter to compare accumulated exposure for different scenarios. For that reason, the ratios of the AUCs of the breast-feeding scenarios and the formula-only scenario are more important than the AUC values themselves; these ratios are shown in Table 4. For example, a ratio for a particular breast-feeding scenario of 6 indicates that the accumulated exposure for that scenario is 6 times that of the formula-feeding only scenario. The ratio can easily be translated to a corresponding measure of percent above or below the baseline scenario of formula-feeding only. For example, if the ratio is 6, this is equivalent to saying that the accumulated exposure for the breast-feeding scenario is 500% higher than the formula-only scenario [(6–1) × 100%]; if the ratio is 0.7, this is equivalent to saying that the accumulated exposure for the breast-feeding scenario is 30% lower than the formula-only scenario [–(0.7–1) × 100%].

The lipid concentrations are predicted to peak at approximately 44 ppt TEQ for the 6-month, 1-year, and 2-year scenarios (Table 4). These peaks uniformly occur at 9 weeks of age. For the 6-week breast-feeding scenario, the peak is 34 ppt TEQ lipid, which occurs at 6 weeks of age. The lipid concentrations decline after these peaks for the breast-feeding scenarios, but the decline is slower as the duration of breast-feeding increases. For the 2-year scenario, the lipid concentration stays near 40 ppt TEQ after 2 years of age (Figure 3). The 6-week scenario shows an increase in infant body lipid concentration to > 30 ppt TEQ, but then shows a rapid decline, so that it follows the formula-only scenario fairly well after 2 years of age. All four scenarios begin to merge near 10 years of age (Figure 2). The rise in concentrations seen in the later years results from the increase of percentage body fat and the subsequent increase in half-life as predicted by the elimination rate model that we used.

The AUC results in Table 4 show the accumulated exposure to be higher for each of the breast-feeding scenarios than for the formula-only scenario. This exceedance after 1 year is about a factor of 6 for breast-feeding for ≥ 6 months. For the first 10 years of life, the accumulated exposure is approximately 2 times higher for breast-feeding scenarios than for the formula-feeding only scenario. The ratios suggest that breast-feeding results in a lifetime exposure only 1.03–1.18 times higher than formula feeding, or from 3% to 18% higher than formula feeding only.

We conducted a sensitivity analysis to evaluate the effect of doubling the mother's body burden, which we assumed would double the dose to the infant as well as the initial body burden of the infant. We used the 6-month scenario for this evaluation and assumed that the dose to the infant would double over those 6 months and that the infant body burden at birth was 20 ppt TEQ instead of 10 ppt TEQ. Also, we included one run in which the initial infant's body burden was 20 ppt TEQ but the dose to the infant was the same as in the initial scenario. This second sensitivity run evaluated only the impact of the initial body burden.

The results of this sensitivity analysis are shown in Figure 4. As expected, the predicted infant body burden peak almost doubles, from 44 ppt TEQ to just under 90 ppt TEQ. The AUC doubles during the 6 months of breast-feeding. However, as expected, this gap narrows over time. After 10 years, the AUC for the elevated exposure is about 43% higher than the baseline 6-month scenario; after 70 years, the difference is only 9%. Figure 4 also shows that the initial body burden assumption has very little effect on modeling results. When only the initial body burden of the infant is increased from 10 to 20 ppt TEQ lipid, the peak concentration at 9 weeks increases slightly to 49 ppt TEQ with the higher initial body burden, but the AUC is only marginally different for the baseline

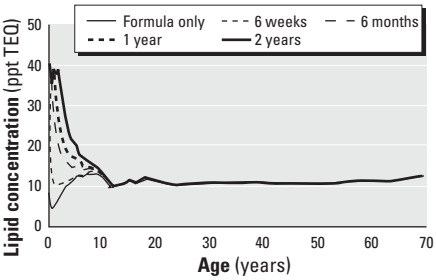


**Figure 2.** Demonstration of the model for evaluating impacts on lipid concentrations of infants resulting from various nursing scenarios during a lifetime.

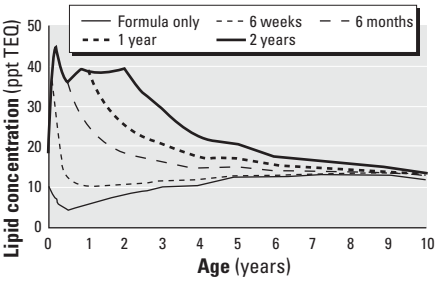


**Figure 3.** Demonstration of the model for evaluating impacts on lipid concentrations of infants resulting from various nursing scenarios during the first 10 years of life.

**Table 4.** Results of pharmacokinetic modeling for formula feeding and four breast-feeding scenarios.

| Description of output | Formula | Breast-feeding scenarios | | | |
|---|---|---|---|---|---|
| | | 6 weeks | 6 months | 1 year | 2 years |
| Peak concentration (pg/g lipid) | 13.0 | 34.1 | 44.3 | 44.3 | 44.3 |
| Peak (time after birth) | 9 years | 6 weeks | 9 weeks | 9 weeks | 9 weeks |
| AUC after 1 year | 2,168 | 5,989 | 12,129 | 13,645 | 13,645 |
| AUC after 10 years | 39,433 | 46,516 | 62,696 | 73,183 | 86,370 |
| AUC after 70 years | 275,419 | 282,654 | 299,304 | 310,210 | 324,202 |
| $AUC_{BF}/AU_{formula}$ | | | | | |
| 1 year | — | 2.8 | 5.6 | 6.3 | 6.3 |
| 10 years | — | 1.2 | 1.6 | 1.9 | 2.2 |
| 70 years | — | 1.03 | 1.09 | 1.13 | 1.18 |

BF, breast-feeding.

6-month feeding scenario. The lack of meaningful impact of the initial infant body burden is also seen in Figure 3, which shows all of the evaluation scenarios. The infant body burden appears to quickly adjust to the dose: a high dose causes the infant body burden to increase quickly and a low dose, such as with formula feeding, causes the infant body burden to drop to a level supported by that dose. In short, the mother's body burden certainly affects the dose received by the child, and although the initial body burden of the infant is also affected (we presume), this does not appear to be critical to the infant's subsequent body burden in the first weeks and months of life.

## Summary and Future Research Needs

In this paper, we evaluated infant exposure to dioxin-like compounds via consumption of breast milk. Limited measurements in the literature showed that breast-fed infants had higher body burdens compared to formula-fed infants by up to one order of magnitude. Levels in breast-fed infants ranged from near 10 ppt TEQ lipid to > 50 ppt TEQ lipid, with levels in infants in a region known to be affected by a nearby source of dioxin release (metals reclamation plant) > 100 ppt TEQ. In contrast, formula-fed infants were almost always < 10 ppt TEQ and, in some cases, < 5 ppt TEQ.

We used a simple, one-compartment PK model to translate the dose of dioxin TEQs received by the infant via breast-feeding to a body burden, expressed as a lipid concentration. The PK model, while simplistic in both structure and assignment of parameters, nonetheless appears to predict TEQ body burdens that are within the range of observed body burdens. In a limited model validation exercise, the model predicted an average infant body burden of 26 ppt TEQ lipid for six infants who had been breast-fed, whereas the average observed body burden for those six infants was 24 ppt TEQ.

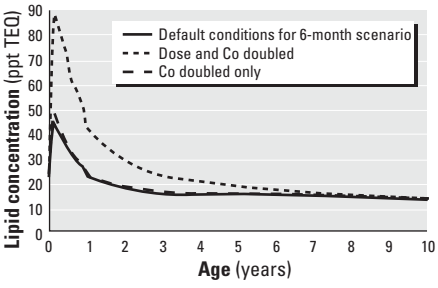


**Figure 4.** Sensitivity analysis showing how a doubling of dose affects the infant body burden for a 6-month breast-feeding scenario and how assuming a higher initial infant body burden affects the infant's body burden during the first 10 years of life. Co, initial TEQ concentration in infant.

We used this modeling framework to evaluate different breast-feeding regimes, including formula feeding only, and breast-feeding for periods of 6 weeks, 6 months, 1 year, and 2 years. First, we calculated temporally varying estimates of dose. Assuming a starting mother's milk concentration of 25 ppt TEQ lipid, we estimated infant doses to be 242 pg TEQ/kg-day at birth and 18 pg TEQ/kg-day after 1 year of breast-feeding. Using the PK model, we predicted that a peak infant concentration of 44 pg TEQ/g lipid would occur at 9 weeks of age. We found that the accumulated exposure to a child who had been breast-fed was significantly higher than a formula-fed only infant (where it was assumed that the infant dose via formula ingestion was similar to typical background exposures for young children). Specifically, ≥ 6 months of breast-feeding would result in accumulated exposure 6 times higher than a formula-fed infant during the first year of life, and this accumulated exposure would still be twice as high after 10 years. Over a lifetime, breast-feeding results in an accumulated exposure that is 3–18% higher than for a formula-fed infant, depending on the length of time of breast-feeding. Using a sensitivity analysis exercise, we demonstrated that the model is linearly responsive to dose received by the infant—doubling of the dose results in a doubling of infant impacts. This sensitivity exercise also showed that the model is relatively insensitive to the initial body burden of the infant. The infant's body burden adjusts very rapidly to the dose received: it declines quickly if the infant receives a low dose, such as from formula-feeding, and rises quickly if the infant has a much higher dose, such as from breast-feeding.

The model parameter of most uncertainty, and of significant impact to model results, is the overall dissipation rate assigned to TEQs. Empirical data in the literature has focused on the dissipation of TCDD in adults, with half-lives typically in the range of 7 years. Our assignment of this parameter for modeling infancy through adulthood was a hybrid of two approaches in the literature developed for PK modeling of TCDD. The model we used for infancy had half-lives < 1 year for this initial period in life, whereas the other model used for adulthood had half-lives from 6 to 20 years. Limited model validation suggested that the dissipation rate of TEQ in the infant was significantly higher (equivalently, the half-life was lower) than implied from data of TCDD in adults.

The U.S. EPA, in its draft reassessment of dioxin and related compounds (*23*), concluded that body burden is the most appropriate exposure matrix for evaluating the health consequence of exposure to dioxin-like compounds. Therefore, although the dose received by the infant via breast-feeding can be tens to even hundreds of times higher than the dose to an adult (on a body weight basis), the resulting body burden of the infant is within the range observed for adults. Specifically, even the peak body burden for the breast-feeding scenarios (44 ppt TEQ) is within a factor of 2 of the average adult body burden of 25 ppt TEQ. This elevation in infant body burden of dioxin-like compounds as a result of breast-feeding has been identified by several researchers in addition to the U.S. EPA (*2,3,4,19,22*); some of these studies have also concluded that the body burdens of breast-fed versus formula-fed infants have merged after a few years (*3,4*). However, the health consequence of this temporary elevation of infant body burdens is uncertain. The U.S. EPA (*23*), along with several others such as the American Academy of Pediatrics (*25*), concluded that the benefits of breast-feeding outweigh any potential risks associated with this practice, and they readily recommend breast-feeding over formula-feeding.

Future work on this PK model should focus on developing congener-specific half-lives that consider not only the differences in the absorption of these congeners in the body but, equally important, the metabolism of these congeners as a function of age. Additional data on infant impacts, such as infant blood TEQ concentrations to study the temporal change in infant body burden during the first weeks and months of life, would also be helpful in future validation of this and similar models.

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