A Generic Toxicokinetic Model for Persistent Lipophilic Compounds in Humans: An Application to TCDD

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Although few toxic chemicals have been studied as extensively as polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), views on their toxicity are still divided, as is reflected by the large variation in tolerable daily intake (TDI) values used by different organizations and governments. For example, the TDI used by the U.S. government is three orders of magnitude lower than that recommended by the World Health Organization (WHO).

Those who doubt the severe toxicity of PCDD/Fs for humans point to the lack of clear effects in epidemiological studies. For example, Smith et al. (1990), giving a review of epidemiological studies concerning occupational and environmental exposures, conclude that the only human effect that can definitely be linked to exposure to 2,3,7,8-TCDD is chloracne. Apparently such an effect is the result of short-term exposures to relatively high concentrations of the causative agent. Smith et al. also state that evidence for long-term effects is weak or not consistent. In most studies, however, exposure was due to a single accident. It is unclear if the internal concentrations of PCDD/Fs in the subjects investigated have been high enough during a sufficiently long period to cause any long-term effects. Furthermore, it might be that effects from exposure to PCDD/Fs appear only after a delay beyond the duration of the studies up to now.

Participants of Operation Ranch Hand form a group that has been exposed to high amounts of 2,3,7,8-TCDD for a period of 1–3 years. These veterans were involved in the spraying of Agent Orange in the Vietnam war. In some of these men TCDD concentrations in blood were still way above background levels, many years after exposure (Michalek et al., 1992). Since this group is also under epidemiological surveillance (Wolfe et al., 1990; Michalek et al., 1990), it may be possible to relate health effects to TCDD levels in blood.

Because epidemiological studies are as yet not decisive, risk assessment of PCDD/Fs is largely based on animal studies. For example, the WHO derived a human TDI from the no-observed-adverse-effect level (NOAEL) of 2,3,7,8-TCDD in rats, taking toxicokinetic interspecies differences into account by a one-compartment human toxicokinetic model. However, a one-compartment model may not realistically describe the internal concentrations of TCDD over a human life span. For example, the partitioning of TCDD in various organs may differ from that in rats, because of differences in organ sizes. Furthermore, both intake and physiological quantities vary with age. Therefore, a more realistic model describing the distribution of TCDD in man is called for.

Physiologically based pharmacokinetic (PBPK) models are well suited to simulating change in internal concentrations. For TCDD, however, they have mostly been developed for the description of distribution in rats, usually on the short term, and they hardly ever account for physiological changes with age (see, e.g., Mills et al., 1992; Leung et al., 1990a).

This paper presents a PBPK model describing the toxicokinetics of TCDD in man during a life span, taking growth and relative changes in body composition with age into account. In view of time scale considerations and the highly lipophilic character of TCDD, the model only contains two
unknown parameters: bioavailability and elimination rate. Because of its general character, the model is applicable to any lipophilic and not rapidly eliminated chemical.

THE MODEL

Model Structure and Assumptions

In the typical PBPK model for rodents, blood flow rates control the amount of compound reaching every organ per unit of time. At equilibrium partitioning coefficients determine the balance between the concentrations in the organs and in that blood. Because the model presented describes the toxicokinetics in man for a complete life span, it differs in several respects from the typical PBPK model.

**Omission of blood flow rates.** Elimination of TCDD is very slow in humans. Michalek et al. (1992) estimated an average half-life of 7.1 years, Wolfe et al. (1994) 11.3 years, and Schlatter (1991) values of 5.2 to 9.7 years, depending on the method used. In rats maximal concentrations of TCDD in rapidly perfused tissues were reached 15 min after administration of a single nonlethal dose. White fat was the slowest in this respect, reaching the maximal concentration after 48 hr (Weber et al., 1993). It is likely that the distribution of a single dose of TCDD is completed within a few hours or days in humans as well. Because our focus is on life span behavior, i.e., on a time scale of years rather than hours or days, we assume a pseudoequilibrium between compartment concentrations at any point of human life. For this reason blood flow can be omitted from the model, so that every compartment contains a certain fraction of the total amount of TCDD present in the body, at any point in time. The fraction depends on the relative organ size, which is age dependent, and on lipid content, as discussed below.

In rats, mice, and hamsters elimination takes place through metabolism in the liver and excretion of metabolites via bile and urine. Unchanged TCDD was also found in the feces of hamsters treated 4–9 days earlier with an intraperitoneal dose of radioabeled TCDD (Gasiewicz et al., 1983). In a human volunteer a small quantity of radioactive material in urine was detectable only shortly after exposure to a high amount of H-labeled TCDD (Poiger and Schlatter, 1986). It may therefore be expected that, in humans exposed to background concentrations, excretion of TCDD through urine is negligible. In the same experiment H activity in feces samples was detectable at least 125 days after exposure, which is long after absorption may be assumed complete. This is probably due to excretion of nonmetabolized TCDD via bile. Since both excretion of bile and metabolism depend on liver size, the model assumes that elimination of TCDD is proportional to liver weight (Wl). Since in most species TCDD-derived radioactivity appears to be eliminated through a first-order process (Gasiewicz et al., 1983), elimination is taken to be proportional to the concentration of TCDD in liver tissue (LA). As the change in the total amount (A) of TCDD in the body as a function of age (a) is given by intake minus elimination rate, we have

\[ \frac{dA}{da} = I - k[A]W_l, \]

where \( k \) denotes the elimination rate constant (time\(^{-1}\)) and \( I \) the intake rate.

Partitioning between compartments. Partition coefficients for separate compartments are usually derived from concentrations simultaneously measured in the particular tissue and blood. In humans the concentrations are usually explained by TCDD–protein binding in the liver. The fact that in humans the concentrations on a lipid weight basis in the liver and in the adipose tissue (Thoma et al., 1990; Leung et al., 1990b) are approximately equal indicates that the amount of TCDD bound to protein in the liver is negligible in persons exposed to background concentrations. However, it might be necessary to account for induction of TCDD-binding proteins in the liver at higher concentrations. Induction in humans will probably occur at higher concentrations than in the rat, because the half-maximal induction in human hepatocytes was found at a 10-fold higher concentration than that in rat hepatocytes (Schrenk et al., 1995).

The concentration in a given compartment \( i \) can now be derived as follows. By definition the lipid fraction of organ \( i \) is given by \( \phi_i = W_{li}/W_i \), where \( W_{li} \) and \( W_i \) denote the weight of the lipid in compartment \( i \) and the total weight of compartment \( i \), respectively. The concentration in compartment \( i \) is then given by

\[ [A_i] = \frac{M_i}{\sum \phi_i W_{li}}, \]  \[ [2]\]

where \( \sum \phi_i W_{li} \) is the total weight of lipid in the body. Equation [1] can be rewritten as

\[ \frac{d}{da} A(a) = I(a) - k \frac{\sum \phi_i W_{li}(a)}{\sum \phi_i W_i(a)} A(a). \]  \[ [3]\]

It follows from Eq. [2] that partitioning over two compartments is determined by the ratio of lipid fractions of these compartments:

\[ \frac{[A_i]}{[A_j]} = \frac{\phi_j}{\phi_i}. \]  \[ [4]\]

Organs with similar fractions of lipid were clustered into one compartment, which resulted in the following compartments: blood (b), muscle (m), adipose tissue (a), bones (bo), liver (l), and “remaining” organs (o). Lipid contents of the compartments were based on literature values (Table 1). Because we did not find information on age dependency of lipid contents of organs, we assume they are constant. The remaining organs compartment consists of a variety of different organs. Since information on lipid contents was found for only some of these, we were forced to use a rough estimate of this compartment’s lipid content. Liver is taken as a separate compartment, because of its role in elimination.

Changes in body composition with age. Physiological magnitudes are approximately constant in short-term modeling, but in life-span modeling they may vary with age. Body weight is the most obvious example, but body composition also changes during ageing. The model accounts for this by age-dependent compartment weights. (Body weight results from the sum
TABLE 1
Lipid Fractions of Human Tissues on Wet Weight Basis

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>f_b</td>
<td>0.0052</td>
<td>Papke et al. (1989)</td>
</tr>
<tr>
<td>Liver</td>
<td>f_l</td>
<td>0.049</td>
<td>Lentner (1981)</td>
</tr>
<tr>
<td>Bone</td>
<td>f_o</td>
<td>0.186</td>
<td>Clarys and Martun (1985)</td>
</tr>
<tr>
<td>Muscle</td>
<td>f_m</td>
<td>0.064</td>
<td>Ryan et al. (1985b), Lentner (1981)</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>f_a</td>
<td>0.859</td>
<td>Beck et al. (1990), Duarte-Davidson et al. (1993), Patterson et al. (1986), Ryan (1986), Ryan et al. (1985b), Schecter et al. (1985)</td>
</tr>
<tr>
<td>Remaining organs</td>
<td>f_r</td>
<td>0.049</td>
<td>Beck et al. (1990), Lentner (1981), Ryan et al. (1985b)</td>
</tr>
</tbody>
</table>

of all compartment weights.) Because body composition differs significantly between males and females, they are modeled separately. Functions of age for organ weights are shown in Fig. 1. Descriptive functions for body weight were fitted to data from a cross-section of the Dutch population (Dutch Ministries of WVC and LNV, 1988; Hulshof and Van Staveren, 1991) (Table 2). Weights at birth (age = 0) described by these regression functions are unrealistically high. Body weights of children under the age of 4 years were therefore described by an exponential function linking up with the regression function.

Adipose tissue weights as percentages of body weight given by Widdowson (1981) for ages 0–17.5 years and by Deurenberg et al. (1991) for ages >18 years were linearly interpolated. Deurenberg et al. give formulas for adipose tissue weight (as percentage of body weight) as functions of age, sex, and body mass index (BMI) for adults and children. BMI was calculated as a function of age by using weights and lengths from the Dutch National Food Consumption Survey (Dutch Ministries of WVC and LNV, 1988; Hulshof and Van Staveren, 1991).

Liver volume as a proportion of body weight declines after the age of 24 years according to Wynne et al. (1989). In their article they give values at the ages of 24 and 91 years, estimated by linear regression analysis. These values were multiplied by a specific weight of 1.06 (g cm⁻³) and by the body weight function discussed above, resulting in liver weight as a function of age. For children only liver weight measurements of babies were found in the literature. The growth of liver weight between 0 and 24 years was assumed to be similar to the body weight curve (Table 2).

For blood, bones, and remaining organs percentages of body weight in adults (Sinclair, 1985) were used to calculate compartment weights at the age of 25 years. Weights of these compartments were taken to be constant from 25 years on. Thus, for adults only weight of the muscle compartment is still unknown. In the model it is set to body weight minus all other compartment weights. Weights of these compartments were calculated with the aid of a statistical exposure model (STEM, see Slob, 1993), from data obtained in the Dutch National Food Consumption Survey (Dutch Ministries of WVC and LNV, 1988; Hulshof and Van Staveren, 1991) and concentration measurements in food around 1991 (Liem et al., 1991). One should realize that concentrations of compounds in food as well as consumption habits may have differed in the past.

Model Input

Because intake through food is estimated to account for 98% of human exposure to TCDD (Travis and Hattener-Frey, 1987), intake rate (I) in the model is determined by consumption of TCDD-contaminated foods. The intake functions used (see Table 2 and Fig. 2) represent age-dependent intakes for a cross-section of the Dutch population around 1987. These functions were calculated with the aid of a statistical exposure model (STEM, see Slob, 1993), from data obtained in the Dutch National Food Consumption Survey (Dutch Ministries of WVC and LNV, 1988; Hulshof and Van Staveren, 1991) and concentration measurements in food around 1991 (Liem et al., 1991). One should realize that concentrations of compounds in food as well as consumption habits may have differed in the past.

Overview of the Model

In our model, the human body is divided into six compartments: blood (b), muscle (m), adipose tissue (a), bones (bo), liver (l), and remaining organs (o). Each compartment has a lipid fraction that is constant over age. Blood flows are not included in the model, because TCDD distribution can...
TABLE 2

Weight and Intake Functions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Symbol</th>
<th>Sex</th>
<th>Equation</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intake</td>
<td>pg day⁻¹</td>
<td>l</td>
<td>♂</td>
<td>A*</td>
<td>5.039</td>
<td>0.02147</td>
<td>9.091</td>
<td>11.621</td>
<td>1.752</td>
</tr>
<tr>
<td>Weight</td>
<td>kg</td>
<td>W</td>
<td>♂</td>
<td>B*</td>
<td>4.495</td>
<td>0.01214</td>
<td>6.735</td>
<td>9.943</td>
<td>1.313</td>
</tr>
<tr>
<td>Blood weight</td>
<td>kg</td>
<td>W₀</td>
<td>♂</td>
<td>B*</td>
<td>0.0307</td>
<td>76.20</td>
<td>3.922</td>
<td>0.4641</td>
<td>13.488</td>
</tr>
<tr>
<td>Bone weight</td>
<td>kg</td>
<td>W₀ₜ</td>
<td>♂</td>
<td>B*</td>
<td>0.1959</td>
<td>57.497</td>
<td>4.617</td>
<td>0.572</td>
<td>11.333</td>
</tr>
<tr>
<td>Liver weight</td>
<td>kg</td>
<td>W₁</td>
<td>♂</td>
<td>B*</td>
<td>0</td>
<td>6.2971</td>
<td>3.922</td>
<td>0.3176</td>
<td>11</td>
</tr>
<tr>
<td>Remaining organ weight</td>
<td>kg</td>
<td>Wᵦ</td>
<td>♂</td>
<td>B*</td>
<td>0</td>
<td>4.99</td>
<td>4.617</td>
<td>0.455</td>
<td>8</td>
</tr>
<tr>
<td>Adipose tissue weight</td>
<td>kg</td>
<td>Wₐ</td>
<td>♂</td>
<td>Linear interpolation (see Fig. 1)</td>
<td>-0.008</td>
<td>1.926</td>
<td>1.926</td>
<td>0.2273</td>
<td>8.666</td>
</tr>
<tr>
<td>Muscle weight</td>
<td>kg</td>
<td>Wₘ</td>
<td>♂</td>
<td>Linear interpolation (see Fig. 1)</td>
<td>0</td>
<td>7.8182</td>
<td>3.922</td>
<td>0.3678</td>
<td>8.4081</td>
</tr>
</tbody>
</table>

* A = a - b(t) + c(1 - EXP(-(t/d)⁻¹)), t is age in years.
* B = at + b(1 + cEXP(-(d(t - e)))⁻¹).
* C = W - W₀ - W₁ - Wₐ - Wₘ - W₀ₜ - W₁.

be considered instantaneous on a time scale of years. The highly lipophilic compound TCDD resides entirely in the lipid fractions of the compartments. At any point in time, the concentration of TCDD on the basis of lipid weight is the same in all compartments. This concentration equals the total weight of TCDD in the body divided by the total body lipid weight.

Changes in the TCDD body burden are governed by the balance between intake and elimination (see Eqs. [1] and [3]). The elimination rate is proportional to liver wet weight and the liver TCDD concentration on a wet weight basis.

In our model, body composition and intake are age-dependent, contrary to conventional models. While the latter models focus on a short time scale, our model describes the kinetics of persistent xenobiotics during the entire human life span.

FIG. 2. TCDD-intake functions, based on a cross-section of the Dutch population. Solid curve, males; dashed curve, females.

COMPARISON WITH DATA

TCDD is a persistent lipophilic compound that has frequently been measured in human tissues. Therefore, we have focused on this compound as a first step in validating the model. Comparison of model predictions to data for other compounds will be discussed in a future paper.

Table 3 summarizes TCDD measurements as found in the literature. Roughly, concentrations on a lipid basis appear to be similar in different compartments, in accordance with the basic assumption of the model. Concentrations measured in the United States are generally somewhat higher than those measured in Germany. Results might differ however because of differences in analytical methods or definition of lipid fraction.

Unknown Parameters

The model as presented here has two unknown parameters: bioavailability and elimination rate. Data giving direct information on these parameters are scarce. Some measurements in infants (Körner et al., 1993) point to a bioavailability of around 97%. Poiger and Schlatter (1986) report 87% absorption of [³H]2,3,7,8-TCDD from the intestine. Their experiment, however, concerned only one person. Better data on bioavailability would have been helpful, although one should realize that uncertainty in the estimate of the intake still remains.

The ideal experiment to measure the half-life of TCDD
TABLE 3

Reported TCDD Concentration Measurements in Unexposed Humans

<table>
<thead>
<tr>
<th>Concentration range</th>
<th>Average</th>
<th>Basis</th>
<th>Comp</th>
<th>Lipid weight</th>
<th>Place/country</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND–20.2</td>
<td>7.0</td>
<td>w</td>
<td>a</td>
<td>ND–23.5</td>
<td>8.15</td>
<td>United States</td>
</tr>
<tr>
<td>1.5–18</td>
<td>w?</td>
<td>l</td>
<td>a</td>
<td></td>
<td>Hamburg, Germany</td>
<td>Beck et al. (1989)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>l</td>
<td>a</td>
<td></td>
<td></td>
<td>Wales, UK</td>
<td>Duarte-Davidson et al. (1993)</td>
</tr>
<tr>
<td>ND–12</td>
<td>4.5</td>
<td>l</td>
<td>b</td>
<td>ND–12</td>
<td>4.5</td>
<td>Steinfurt, Germany</td>
</tr>
<tr>
<td>2.2–20.5</td>
<td>8.4</td>
<td>w?</td>
<td>a</td>
<td></td>
<td>Missouri</td>
<td>Graham et al. (1986)</td>
</tr>
<tr>
<td>ND–14</td>
<td>5.64</td>
<td>w?</td>
<td>a</td>
<td></td>
<td>United States</td>
<td>Gross et al. (1984)</td>
</tr>
<tr>
<td>0.16–5.39</td>
<td>0.98</td>
<td>w</td>
<td>l</td>
<td>3.27–110</td>
<td>20</td>
<td>St. Louis, Missouri</td>
</tr>
<tr>
<td>2.18–19.6</td>
<td>9.08</td>
<td>w</td>
<td>a</td>
<td>2.54–22.8</td>
<td>10.57</td>
<td>St. Louis, Missouri</td>
</tr>
<tr>
<td>2.6–33</td>
<td>12.7</td>
<td>l</td>
<td>a</td>
<td>2.6–33</td>
<td>12.7</td>
<td>Japan</td>
</tr>
<tr>
<td>1.3–9.4</td>
<td>3.4</td>
<td>w</td>
<td>l</td>
<td>26.5–191.8</td>
<td>69.4</td>
<td>Japan</td>
</tr>
<tr>
<td>6–18</td>
<td>9</td>
<td>w</td>
<td>a</td>
<td></td>
<td>Japan</td>
<td>Ono et al. (1986)</td>
</tr>
<tr>
<td>&lt;0.98–15.1</td>
<td>5.38</td>
<td>w?</td>
<td>a</td>
<td></td>
<td>United States</td>
<td>Orban et al. (1994)</td>
</tr>
<tr>
<td>&lt;1.5–9.1</td>
<td>4.0</td>
<td>l</td>
<td>b</td>
<td>&lt;1.5–9.1</td>
<td>4.0</td>
<td>Germany(?)</td>
</tr>
<tr>
<td>3.2–21.3</td>
<td>9.6</td>
<td>l</td>
<td>a</td>
<td>3.2–21.3</td>
<td>9.6</td>
<td>United States</td>
</tr>
<tr>
<td>0–9</td>
<td>3</td>
<td>w?</td>
<td>a</td>
<td></td>
<td>Sweden</td>
<td>Rapp et al. (1986)</td>
</tr>
<tr>
<td>&lt;2.0–17.8</td>
<td>7.4</td>
<td>w?</td>
<td>a</td>
<td></td>
<td>Canada</td>
<td>Ryan et al. (1985a)</td>
</tr>
<tr>
<td>6.4</td>
<td>w</td>
<td>a</td>
<td></td>
<td></td>
<td>Canada</td>
<td>Ryan et al. (1986)</td>
</tr>
<tr>
<td>&lt;3.2–9.7</td>
<td>6.6</td>
<td>l</td>
<td>a</td>
<td>&lt;3.2–9.7</td>
<td>6.6</td>
<td>Japan</td>
</tr>
<tr>
<td>3.7–8.3</td>
<td>4.3</td>
<td>w</td>
<td>a</td>
<td>4.3–9.7</td>
<td>New York</td>
<td>Schecter et al. (1985)</td>
</tr>
<tr>
<td>18</td>
<td>w</td>
<td>a</td>
<td></td>
<td></td>
<td>South Vietnam</td>
<td>Schecter et al. (1986)</td>
</tr>
<tr>
<td>6.4</td>
<td>w</td>
<td>a</td>
<td></td>
<td></td>
<td>Canada</td>
<td>Schecter et al. (1986)</td>
</tr>
<tr>
<td>10</td>
<td>w</td>
<td>a</td>
<td></td>
<td></td>
<td>Canada</td>
<td>Schecter et al. (1986)</td>
</tr>
<tr>
<td>7.2</td>
<td>w</td>
<td>a</td>
<td></td>
<td></td>
<td>New York</td>
<td>Schecter et al. (1986)</td>
</tr>
<tr>
<td>7.1</td>
<td>l</td>
<td>a</td>
<td></td>
<td></td>
<td>Canada</td>
<td>Schecter et al. (1987)</td>
</tr>
<tr>
<td>5.7</td>
<td>l</td>
<td>p</td>
<td></td>
<td></td>
<td>United States</td>
<td>Schecter et al. (1991)</td>
</tr>
<tr>
<td>6.9</td>
<td>l</td>
<td>a</td>
<td></td>
<td></td>
<td>United States</td>
<td>Schecter et al. (1991)</td>
</tr>
<tr>
<td>2.9–5.1</td>
<td>4.0</td>
<td>l</td>
<td>b</td>
<td>2.9–5.1</td>
<td>4.0</td>
<td>Germany</td>
</tr>
<tr>
<td>3.2–6.5</td>
<td>5.1</td>
<td>l</td>
<td>a</td>
<td>3.2–6.5</td>
<td>5.1</td>
<td>Germany</td>
</tr>
<tr>
<td>1.2–12</td>
<td>4.62</td>
<td>l</td>
<td>b</td>
<td></td>
<td>Germany</td>
<td>Schrey et al. (1993)</td>
</tr>
<tr>
<td>&lt;1–10</td>
<td>5.0</td>
<td>?</td>
<td>a</td>
<td></td>
<td>United States</td>
<td>Stanley et al. (1986)</td>
</tr>
<tr>
<td>ND–18.2</td>
<td>3.2</td>
<td>w?</td>
<td>a</td>
<td></td>
<td>3.7</td>
<td>Munich, Germany</td>
</tr>
<tr>
<td>1.1</td>
<td>?</td>
<td>l</td>
<td></td>
<td></td>
<td>Munich, Germany</td>
<td>Thoma et al. (1989)</td>
</tr>
<tr>
<td>2.6–18.0</td>
<td>8</td>
<td>w?</td>
<td>a</td>
<td></td>
<td>9.3</td>
<td>Munich, Germany</td>
</tr>
<tr>
<td>1.0–88.9</td>
<td>16.4</td>
<td>w</td>
<td>l</td>
<td></td>
<td>Munich, Germany</td>
<td>Thoma et al. (1990)</td>
</tr>
</tbody>
</table>

* All concentrations are given in pg/g (ppt).

w, pg/g wet wt; l, pg/g lipid weight.

a, adipose tissue; b, blood; l, liver; p, blood plasma.

Concentration in pg/g lipid weight. Concentrations based on wet weight are divided by lipid content. Lipid contents used were blood 0.0052, liver 0.049, bone 0.186, muscle 0.064, adipose tissue 0.859, and remaining organs 0.049.

was performed by Schlatter (1991), whose volunteer ingested a single dose of TCDD. This experiment resulted in an estimated half-life of 9.7 years for adipose tissue. However, it remains unclear if this value is representative for the whole human population. Measurements in Vietnam veterans relate to a large number of individuals, with an estimated half-life of 7.1 years (Michalek et al., 1992) based on 36 persons or 11.3 years based on 337 persons (Wolfe et al., 1994). Flesch-Janys et al. (1994) report a median half-life of 6.9 years, based on measurements in blood of 48 persons. All these half-lives were estimated on the assumption of an exponential decay of the internal concentration to respective background levels of nil (for [H]2,3,7,8-TCCD, Schlatter), 4 pg/g (Michalek et al.), 4 pg/g (Wolfe et al.), and nil (Flesch-Janys et al.). Strictly, the implied steady-state conditions do not hold because both the intake and the constitution of the human body depend on age. If we ignore this however, the elimination rate constant k, referring to the amount in the liver in the present model (see Eq. [1]), is related to the half-life (t½) by

\[
k = \frac{\sum W_{ki} \ln 2}{f_i W_i t_{1/2}}.
\]

[5]

Since Wolfe's estimate is based on the largest amount of
data we use 11.3 years as an estimate for half-life. The median age of the subjects was about 43 years. At that age \( \sum \frac{W_d}{t - W_p} \) (which is age-dependent in the model) equals about 255. This results in a rough estimate for the elimination rate constant of \( k \approx 15.6 \text{ year}^{-1} \).

Age-Dependent Data

As the model aims at describing the internal concentration over a human life span, measurements of internal concentrations at different ages are needed for validation of the model. An accurate set of longitudinal data (i.e., the same individuals followed in time) would have been ideal, but is not available. Several cross-sectional studies have been done, however, and from these the data from Schrey et al. (1993) are the most appropriate for our purposes, comprising 95 TCDD measurements in blood samples from a homogeneous population under background conditions with ages ranging from 12 to 82 years. Therefore, we have chosen this set of data for further analysis.

For our model simulations we used the intake function described earlier. This function was based on Dutch data. Concentrations of TCDD in blood of 18 Dutch persons did not indicate systematic differences between the Dutch and the Schrey et al. population.

When we set bioavailability at 100\% and the elimination rate constant \( k \) at 15.6 year\(^{-1}\), the model simulation did not describe the data satisfactorily (see Fig. 3). The model could only mimic the measured increase in concentrations with age for \( k \) equal to zero. This value appears unrealistic, given the decrease in concentrations in exposed individuals reported in the literature (e.g., Flesch-Janys et al., 1994; Wolfe et al., 1994; Schlatter, 1991).

Intake History

The model calculations underlying Fig. 3 concern the simulation of a single individual, i.e., a single intake function (of age) is transformed into a single internal concentration function (again of age). The data, on the other hand, relate to different individuals with different ages and therefore having different intake histories. It is known that emissions of TCDD have been different in the past.

Sediment and archived soil sample data indicate that around the year 1940 the concentrations of dioxins and furans in the environment began to rise. Data collected by Cruczwa and Hites (1984) and Kjeller et al. (1990) suggest a more or less logistic increase of concentrations in the United States and the United Kingdom until at least 1960. After 1960 a slight decrease in environmental concentrations may have occurred. The data that were collected by Friege and Klos (1990) in Germany denote a sharp increase from 1940 to 1960, followed by a slow drop of the concentrations. Beurskens et al. (1994) report measurements of TCDD in a Dutch lake’s sediment dated from 1945, 1965, and 1985. In the oldest core TCDD was below detection level, and in the 1965 core the level was 36 times as high as in the 1985 core. The time trend in this lake indicates a much sharper drop of TCDD levels after 1965 than in the other data discussed.

In addition to concentrations in foods, dietary habits have changed in the course of time. For example, consumption of a number of TCDD-containing foods like milk (products) and edible fats has decreased between 1960 and 1985 in middle-aged men, while intake of cheese has increased (Kromhout et al., 1990). There has been a shift to higher consumption of foods connected with a healthy life-style, which includes for example consumption of low-fat milk products. Furthermore, shifts from consumption of animal fat (lipids) to vegetable fat have probably had considerable influence on TCDD intake, since concentrations of PCDD/ Fs in animal fats are higher than in vegetable fats (Theelen et al., 1993).

In the model calculations illustrated by Fig. 3 environmental concentrations of TCDD in the past were assumed to be constant. To allow for different exposures in the past the intake function was multiplied by a time-dependent correction factor \( F(t) \). This results in the following description of the total amount of TCDD in the body of individuals born at time \( t_b \):

\[
\frac{d}{da} A(a; t_b) = F(a + t_b) I(a) - \frac{\sum f_i W_i(a)}{\sum f_i W_i(a)} A(a; t_b), \quad [6]
\]

where \( a + t_b \) is real time.

Schrey et al.’s blood samples were collected in 1991. If the intake function, derived from Dutch data collected in 1988, is used to describe the intake of the German population, the correction factor \( F(t) \) should equal unity around 1988. If bioavailability is less than 100\%, this value is lower.

A simulated cross-section of the population was obtained.
by starting a series of simulations at \( t = 1922 \) to \( t = 1991 \), with a time step of 1 year between the starts of the consecutive simulations. Simulations were started at birth, where the total amount of TCDD in the body was assumed to be negligible (\( A(0, t) = 0 \)). The concentrations in blood lipid at \( t = 1991 \) form the simulated cross-section of the population (age \( 0 \) to 69 years).

A function for \( F \) was used that could exhibit a variety of shapes (see the appendix). Optimization of parameter values describing this function was done by fitting the simulated cross-section of the population to Schrey et al.'s measurements using a weighted least-squares method (weights were set inverse to squared measurements).

When three of the parameters were estimated simultaneously, allowing the function to adopt a large variety of shapes, a sharply decreasing function for \( F \) was obtained. Although the model fitted the data well, the obtained function for \( F \) appeared unrealistic in view of the TCDD concentrations measured in the environment. Therefore, we rejected this result.

Fitting the model with the elimination rate constant fixed at 15.6 (year\(^{-1}\)) and varying the height of \( F \), the occurrence of its maximum fixed at 1960, resulted in a good description of the data for people up to the age of 50 years. The function \( F \) was higher at the best fit for females than for males. It seems unrealistic, however, that the historical changes in intake for males and females differ. A possible cause of the dissimilarity found is a difference in elimination rates between males and females. This concept is purely hypothetical, as we have no empirical data to support this hypothesis. If we assume there is a difference, however, the correct height of the function for \( F \) should be the one obtained by fitting for males, since the elimination rate constant we used was based on data in males (Ranch Hand veterans). A fit of the model for females with use of the correction function as found for males (Fig. 4B) by varying the elimination rate resulted in an elimination rate constant of 12.0 (year\(^{-1}\)). This fit is shown in Fig. 4A, together with the best fit for males. The resulting function \( F \) shows a decrease after 1960 that is steeper than the change in environmental concentrations suggested by most of the time-trend data. However, the correction factor reflects changes not only in environmental concentrations but also in dietary habits.

**Elimination rate.** Uncertainty about the value of the elimination rate constant remains. The value we used was calculated from a half-life derived by assuming exponential decline of concentrations in human tissues to a steady-state background level after exposure to high levels of TCDD earlier in life (Ranch Hand veterans). Since this assumption does not hold we performed a model simulation in which an extra dose of TCDD was given during 1 year at the age of 30 years. Calculation of the elimination rate constant from the simulated concentrations in blood at ages 41 and 46 years under the exponential decline assumption resulted in an overestimation of the elimination rate set in the model. Consequently, the value we used in the model is probably an overestimation of the elimination rate. Fitting the model with the obtained function \( F \) for males by varying the elimination rate constant resulted in a lower value \( (k = 15.2 \text{ year}^{-1}) \). This seems to confirm the conclusion that an elimination rate constant of 15.6 year\(^{-1}\) is an overestimation. One should be careful of drawing conclusions from this result, however, because the height of the correction factor \( F \) and the value of the elimination rate constant are coupled and cannot be estimated independently from a set of cross-section data.

**Breastfeeding**

Intake due to breastfeeding was not accounted for in the model simulations presented here. In industrialized countries...
concentrations in human milk can cause high levels of intake in infants. If we assume an intake of 91 pg/day during the first 90 days of life, 7.1 pg/day in the next 275 days, and according to the intake function of Table 2 later on, simulated concentrations are substantially elevated until the age of 12, compared to the simulations presented in Fig. 3. Because TCDD measurements in children were not available, the model could not be validated for children under the age of 12 years.

For the mother, breastfeeding constitutes an extra source of elimination from her body. To model the extra elimination by breastfeeding we assumed that the concentration of TCDD in the lipid fraction of the milk is equal to the concentration of TCDD in all other lipid fractions in the body. The model for a breastfeeding woman is

\[
\frac{d}{da} A(a; t_b) = F(a + t_b) I(a) - k \sum_j f_j W_j(a) A(a; t_b) - m(a) \frac{A(a; t_b)}{\sum_j f_j W_j(a)}. \tag{7}
\]

The excretion rate of milk-lipid \( m(a) \) was set to 30 g/day during breastfeeding, which was assumed to last for 90 days following the birth of each child. Otherwise, \( m(a) \) was set to zero. The decrease in TCDD concentration in blood-lipid caused by breastfeeding as many as four children is small compared to the variation in the population measured by Schrey et al. (1993) (see Fig. 6).

**Prediction of Future Concentrations**

One of the applications of the model is to predict future concentrations in human tissues under certain conditions, for example in relation to policy measures. To illustrate this, we made a prediction for the case that environmental concentrations and dietary habits remain at the level of 1987 \((F = 1)\), i.e., we assumed that the intake function described in Table 2 remains valid in the future. The predictions (Fig. 5) show a small decrease in concentrations in persons who were older than 40 years in 1991. Concentrations in younger persons will increase and approach a maximum of 3.5 pg/g at the age of 70 years. It should be noted, however, that future concentrations depend greatly on the values of the correction factor for historical intake and the elimination rate constant.

**DISCUSSION**

Although the model presented is basically very simple, the dynamics of the body make it nontrivial. For example, it is not immediately clear whether an increase in adipose tissue weight occurring in fattening persons will result in an increase or a decrease of internal concentrations of TCDD. On the one hand, a larger adipose tissue weight leads to dilution of the compound in the body. On the other hand, a smaller fraction of the total body burden will be available for elimination, a larger fraction being located in the adipose tissue.

Compounds that are eliminated very slowly seem relatively easy to model because short-term fluctuations (e.g., in intake) effectively smooth out and can be omitted. The present paper, however, shows the other side of the coin: long-term changes in environmental concentrations cannot be ignored for these compounds and need to be accounted for. In the present study changes in environmental concentra-
tions were corrected for by introducing a correction function \( F \). This function combines changes in concentrations in foods with changes in dietary habits. We expect that TCDD concentrations in foods were maximal around 1960, as indicated by the PCDD/F concentrations in sediment and soil samples. However, the relation between TCDD concentrations in foods and PCDD/F concentrations in sediment and soil samples might be complicated. Furthermore, we had little information about changes in dietary habits. Consequently, it is uncertain what the correction function \( F \) for TCDD should look like. Though we fitted the model, while optimizing for a number of parameters of this function, the resulting function for \( F \) as presented in Fig. 4B is only one of the functions possible. For example, fitting the model with a different value for the elimination rate constant \( k \) will lead to an equally good fit, but with a different correction function.

Although the model described the cross-section of concentrations in blood lipid reasonably well, it underestimated the concentrations at ages >50 years. We will discuss several possibilities that might cause the latter result. Reported estimates of TCDD's half-life from measurements in temporarily highly exposed individuals are usually based on the assumption that internal concentrations exponentially decline to a steady-state background level (e.g., Michalek et al., 1992; Wolfe et al., 1994; Schlatter, 1991; Weber et al., 1993). We showed, however, that the latter assumption does not hold, because the intake function is not constant with time and age, and the constitution of the body changes with age, while the half-life of TCDD is large. Therefore, the reported elimination rates are probably overestimates, as discussed above. Clearly, with a lower elimination rate, the fit of the model would improve.

The mechanism of elimination of PCDD/Fs in humans is still obscure. In the present model, first-order elimination from the liver was assumed. This could either be through metabolism or excretion via the bile and feces. Elimination might decrease with age, due to a decrease in functional liver weight, in metabolic activity, or in bile production. When we assumed elimination in ageing people to be lower by a factor of two, the model fitted the data well over the whole human life span. However, we did not find clear evidence in the literature indicating such a decrease in elimination rate. Levels of cytochrome P450, which are thought to be connected with TCDD metabolism in rats, do not decrease with age in humans (Schmucker et al., 1990). Also no data were found indicating that bile flow rate decreases with age. Therefore, we sustain to a constant elimination rate in humans as long as evidence to the contrary is lacking.

The adipose tissue, which constitutes a high capacity for TCDD storage, has a great influence on the distribution of TCDD. Consequently, if adipose tissue weights as used in the model are unrealistic, erroneous predictions for other compartments, including blood, can be the result. Data concerning adipose tissue weight as a percentage of body weight reported by Durnin and Womersley (1974) differ somewhat from the data used in the model (for ages >17 years). Using these data improved the fit, but only slightly. Because the functions we used in the model link up better with the data on adipose tissue in children, we decided not to change the model in this respect.

**Protein binding.** Protein binding is ignored in the model. If protein binding of TCDD is substantial, in reality, distribution over the compartments is not described accurately by the model since the relative protein fractions differ between compartments. Also, concentrations in blood, containing considerable protein, will be underestimated by the present model, but for all ages to the same extent. As discussed earlier, binding to inducible proteins in the liver is not considered either, because induction in humans is thought to be negligible at background intakes. To simulate protein induction, the model could be expanded with an Ah receptor-mediated induction mechanism (e.g., see Leung et al., 1990a; Carrier et al., 1995).

Although the present paper addresses the behavior of the average individual, the model is also suitable for evaluating particular individuals. Thus, the model can give clues for understanding the large interindividual variation in internal concentrations that is typical for human data. For example, one might hypothesize that variation in intake caused by individual dietary habits is an important factor here. However, when it is assumed that body weight is correlated with intake (which is likely for lipophilic compounds), the effect of a higher intake will be counteracted by a larger body volume. Indeed this phenomenon was found in model simulations. Furthermore, an analysis of the regression residuals of the measured concentrations in blood did not show any correlation with body weight or body mass index. At present we are further investigating interindividual variability.

**Uncertainties.** The main uncertainty in the present analysis concerns the correction function for the intake history, determined by changes in environmental concentrations and in dietary habits over the past decades. Because data on these changes are rather scarce, we reconstructed the correction function from the relation of TCDD blood levels with age, assuming a value for TCDD's half-life as reported by Wolfe et al. (1994). The problem is that the reconstruction of the correction function is highly dependent on the value of the elimination rate constant used. By the same token, the estimate of the elimination rate constant from Wolfe et al. may not be completely adequate, because intake history (in the general population) was not taken into account in their analysis. We are at present examining the possibility of estimating the elimination rate from the data of Wolfe et al. (1994) using our model instead of the steady-state assumption.
APPENDIX

The total amount ($A_i$) of a given compound in compartment $i$ is given by the sum of the amounts in the lipid fraction ($A_{f,i}$), the water fraction ($A_{w,i}$), and the remaining fractions ($A_{r,i}$). If the amount of compound in the remaining fractions is negligible ($A_{r,i} = 0$), only the water and lipid fractions are of importance. (We assume this is the case for TCDD, which implies that the amount bound to proteins is negligible for TCDD in humans.)

Suppose that the ratio of concentrations in both fractions is given by the octanol–water partition coefficient ($K_{ow}$):

$$K_{ow} = \frac{[A_{f,i}]}{[A_{w,i}]},$$

where $[A_{f,i}]$ is the concentration in the lipid fraction, $[A_{w,i}]$ the concentration in the water fraction, $W_{f,i}$ the compartment’s water weight, and $W_{w,i}$ the lipid weight. The amount is then given by

$$A_i = A_{f,i} + A_{w,i} = \frac{A_{f,i}W_{w,i}}{K_{ow}W_{f,i}} + \frac{A_{w,i}W_{f,i}}{K_{ow}W_{w,i}}.$$  

If $K_{ow} \gg W_{w,i}/W_{f,i}$, the total amount in compartment $i$ is determined by the amount in the lipid fraction of that compartment, the amount in the water fraction being negligible. In this case the concentration ($[A_i]$) in compartment $i$ is given by

$$[A_i] = [A_{f,i}] = \frac{W_{f,i}}{W_i} \times \left(1 + \frac{W_{w,i}}{W_{f,i}}\right).$$

where $W_i$ is the compartment’s weight.

Correction Factor

The correction factor we used for time-dependent changes in intake, due to historical changes in concentrations in food products and eating habits, $(F(a + t_0))$, is represented by

$$F(a + t_0) = A + HC\left(\frac{G - (a + t_0) + 1922}{B}\right)^{C-1} \times \exp\left(-\left(\frac{G - (a + t_0) + 1922}{B}\right)^C\right),$$

where parameters $A$ and $H$ affect the functions height, parameter $B$ scales the function over the time axis, parameter $G$ shifts the function over the time axis, and parameter $C$ determines the shape of the function.

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A HUMAN TOXICOENETIC MODEL


