A human toxicokinetic model for dioxin

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1. Introduction

We have developed a toxicokinetic model describing the distribution of lipophilic toxicants in the human body during a lifetime[1]. Since the intake rate, body weight and body composition cannot be assumed constant over a lifespan, we use age-dependent intake, and age-dependent compartment weights. Historical changes in the intake rate due to changes in concentrations in foods and eating habits are considered as well. In this paper we show an application of this model to dioxins, in particular to TCDD.

2. The model

The model divides the body into several physiological compartments, their weights being functions of age (see Fig.1). Because elimination of dioxins and furans is very slow compared to the kinetics of distribution over the body, ingested TCDD is assumed to be instantaneously distributed over all compartments.

The elimination probably takes place by metabolism in the liver, or through excretion of bile. Since both processes depend on liver size, the model assumes elimination to be proportional to liver weight. The elimination rate is congener dependent.

Since in most species TCDD-derived radioactivity appears to be eliminated through a first-order process[2], elimination is assumed to be proportional to the concentration in liver tissue.

Intake rate in the model is determined by consumption of foods contaminated by dioxins and furans. The model input is given by functions describing the age-dependent intake rates of dioxins and furans for the entire (Dutch) population (as an example the intake rate of TCDD is shown in Fig.2). These intake functions were calculated with the aid of a statistical exposure model[3], using food consumption survey data[4,5] combined with concentration measurements in food[6]. Bioavailability was assumed 100%.

Since the change in the total amount (A) of compound in the body as a function of age (a) is given by intake minus elimination rate, we have

$$\frac{d}{da}A(a) = I(a) - k\ C_l(a)\ W_l(a),$$

where I denotes the intake rate, k the elimination rate constant, C_l the concentration in the liver and W_l the weight of the liver.

Because the compounds are extremely lipophilic, the amount of compound in any compartment can be assumed to be determined by the lipid fraction. Assuming that the lipid fractions of all compartments have the same solubility, the concentrations based on lipid weight will be equal in all compartments at semi steady-state.

We assume protein binding in the liver at background concentrations to be negligible. For TCDD this is in accordance with findings by Thoma[7] and Leung[8] who found approximately equal concentrations in liver and adipose tissue on a lipid weight base.

The concentration in the liver is now given by:

$$C_l = \frac{Af_l}{\sum_j W_{f,j}},$$

where f_l denotes the lipid-fraction of the liver, and $\sum_j W_{f,j}$ the total body lipid weight.

The concentration on a lipid weight base in any compartment i ($C_{f,i}$) is given by:

$$\frac{d}{dt}C_{f,i}(t) = \frac{I(t)}{\sum_j W_{f,j}(t)} - k\ \frac{W_{f,l}(t)}{\sum_j W_{f,j}(t)}\ C_{f,i}(t) - \frac{C_{f,i}(t)}{\sum_j W_{f,j}(t)}\ \frac{d}{dt}\sum_j W_{f,j}(t),$$

where $W_{f,l}$ denotes the lipid weight of the liver.

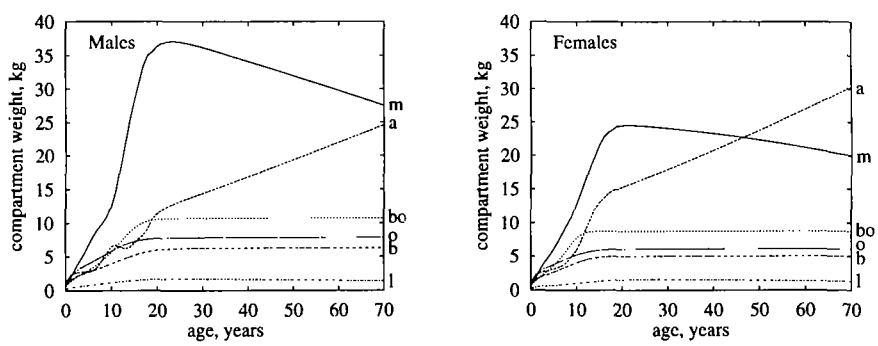

Figure 1. Weights of all compartments. m = muscle, a = adipose tissue, bo = bones, o = 'remaining' organs, b = blood, l = liver.

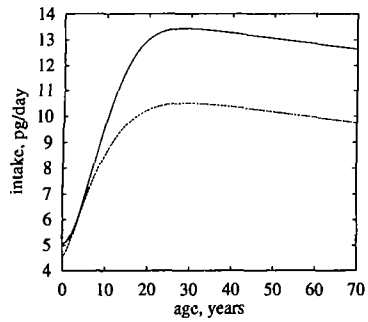

Figure 2. TCDD-intake functions, based on a cross-section of the Dutch population. Solid curve: males, dashed curve: females.

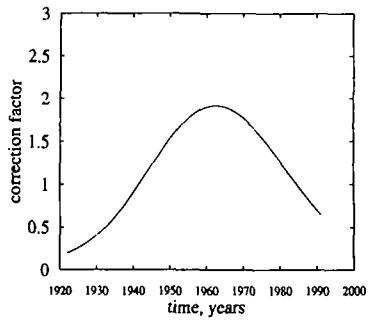

Figure 3. Correction function for the history of the intake rate.

3. Results

As the model aims at describing the internal concentrations over a human life span, measurements of internal concentrations at different ages are needed for validation of the model. Since there was no accurate set of longitudinal data available, we used a cross-sectional study. An appropriate data set of this type has been collected by Schrey *et al.*[9], who have measured dioxin and furan concentrations in blood-lipid over a wide range of ages. We calibrated the model for the TCDD data of this study.

For TCDD a half-life of 11.3 years was found by Wolfe *et al.*[10]. This value corresponds roughly with an elimination rate constant (k) of 15.6 year^{-1}. With the elimination rate constant set at 15.6 year^{-1} the model did not describe the data satisfactorily. It 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 temporarily highly exposed individuals reported in the literature (e.g.[10]).

In these simulations the intake history was assumed equal for all persons. However, the ages of the simulated persons range from 12 to 70 years, and their intake histories may have differed considerably. It is known that emissions of dioxins and furans have differed in the past. Based on data on sediment and soil samples we constructed a time-dependent correction function for the history of the intake rate (Fig 3). Data from these samples indicate that environmental concentrations have risen sharply around 1940, and may have decreased after reaching a peak around 1960. The height of this peak was determined by fitting age-specific model simulations to the cross-sectional data. For TCDD the model simulations now describe the data well for people up to the age of 50 years.

With use of the history (correction) function found for TCDD, and the congener dependent intake functions the data for all congeners collected by Schrey *et al.*[9] could be described well with model simulations by adapting the congener-specific elimination rate. In this way, elimination rates can be estimated for all congeners.

It should be noted that a lot of uncertainty remains about the history (correction) function, and the functions may not be the same for all congeners. Apart from changes in environmental concentrations, affecting concentrations in foods, there have also been changes in eating habits. We believe these changes also affect intake rate, but the relation is not exactly clear.

4. Conclusions

Model simulations have shown that historical changes in intake, due to changes in environmental concentrations and in dietary habits, greatly influence the relation of TCDD concentrations with age at background intake. At constructing prognoses, and in the analyses of historical data these historical changes should be accounted for. Historical changes in intake may even influence estimates of elimination rates when longitudinal data are used (e.g.[11),12)]) especially from data near background levels.

5. Applications

A major application of this model is the prediction of future concentrations in human tissues at a given intake level. For example, future concentrations in breast-milk at a proposed tolerable daily intake (TDI) can be calculated. In this way the future exposure of infants can be predicted, and controlled. An example is shown in Fig. 4 where future concentrations in women are predicted at three different levels of exposure.

In trend studies some doubt usually remains whether observed changes are really due to structural changes in the general population, or to other causes. Our model can be used to support the findings of such studies.

The model might also be useful for risk assessment purposes. For example, it can be used to find the intake rate leading to internal concentrations in humans that have been found to be associated with health effects in animal studies. Or, when mechanisms of action for dioxins and furans are better understood, these could be implemented in the model.

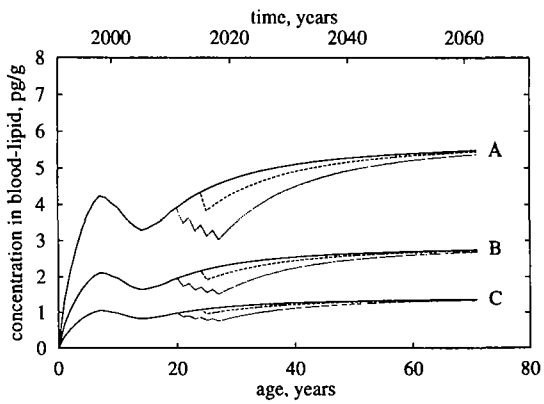

Figure 4. Model simulations of breast-feeding females with an elimination rate constant (k) of 15.6 year^{-1} for elimination from the liver. The intake was set at three different levels: twice the level measured in 1991 (labelled A), at the level measured in 1991 (labelled B) and at half the level measured in 1991 (labelled C). Excretion of milk-lipid was set to 30 g/d during breast-feeding periods of 90 days per child. Solid curve: female with no children. Dashed curve: female who breast-feeds one child at the age of 24 years. Dotted curve: female who breast-feeds children at the ages of 20, 22, 24 and 26 years.

6. Acknowledgments

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7. References

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