TCDD kinetics in Seveso patients

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Introduction

The object of this study is to investigate TCDD kinetics in humans using data collected on the patients exposed at the Seveso site in 1976. The approach is based on a previously validated model of TCDD on rats and monkeys and PCDFs in humans (Carrier *et al*., 1995a,b). This is warranted since it is known that all these molecules share a common Ah receptor $(A_h R)$-mediated mechanism of toxic and biological responses (Safe, 1986; Birnbaum, 1994; Pohjanvirta and Tuomisto, 1994; Van den Berg *et al*., 1994; Hankinson, 1995; Santostefano *et al*., 1998.)

One of the essential features of the model is the nonlinear response to doses. This non linearity stems mainly from the differential fractionating between liver and adipose tissue as a function of instantaneous body concentration at that very moment: $C_b(t)$=body burden/body weight. When the body concentration is high , the fraction of the body burden in the liver is high, while at low concentrations it is much lower. Since, in general, body concentration varies with time so will the fractionating. This feature can be described heuristically with only three basic constants: the minimum and maximum fractions ($f_h^{\min}$ and $f_h^{\max}$) of the body burden contained in the liver, associated respectively with near zero body burden and very high body burden, and a body concentration constant (K)specifying the mid point between the two above plateaus. These constants are specific to each specie and to each PCDD/PCDF molecule. This has been established experimentally, see figures 1 and 2.

The physiological basis of this non linear fractionating between liver and adipose tissue is driven by the linkage of PCDDs/PCDFs to a protein believed to be mainly CYP1A2 (Santostefano *et al*. 1998) which itself is induced by the presence of PCDDs/PCDFs .

The model further assumes that instantaneous elimination by the liver is proportional to its burden (Leung *et al*. 1988 and 1990; Andersen, 1990). We refer to this proportionality constant as k_e . However, since this liver burden is an ever changing fraction of the overall body burden, the net

result is an overall elimination rate which is a nonlinear function of the body concentration. Thus it is impossible to refer to the concept of constant half life for body burden elimination.

Since the essentials of the above, rest on body concentrations and a varying fractionating of body burden between liver and adipose tissue as a function of body concentration, it is important to factor in the evolution of the anatomic parameters of each subject (sex, body weight, fraction of that weight made up of adipose tissue, fraction made up by the liver, etc.). The model is designed to take into account the evolution of these parameters at each stages of the subject's life; either directly if they are provided, or alternatively, from standard life tables for the population of the country of occurrence. The model incorporates the variations of doses with time through background as well as through any sharp accidental exposures.

Methods

Of the hundreds of Seveso cases followed by Mocarelli *et al*, ten were chosen, for the time being, as illustrative of very different situations: male vs female, children vs adults, low vs high doses. Children are especially interesting to follow, because of their important changes in body weight over the years and the rapid changes of adolescents proportion of adipose tissue; these changes act to dilute overall concentrations and shift the body fraction of adipose tissue.

Mocarelli et al. Needham and Patterson have provided detailed data on Seveso patients: sex, and weight, height and lipid based blood concentrations at different ages post accident from 1976 to 1994. Also available was a measure of average adipose tissue TCDD concentration for the Italian population. The model enabled us to estimate, for each patient, the absorbed dose at the time of the accident, starting from the concentration in blood lipids. From this, the time evolution of the body, liver and tissue concentrations can be predicted.

Since no direct measures of liver TCDD concentrations are available from the Seveso patients nor other human sources, the parameters for the fractionating between liver and adipose tissue were estimated from past data:

1. for $f_h^{\min} = 0.01$ and $f_h^{\max} = 0.69$, we used the values obtained with another high affinity molecule 2,3,4,7,8-PenCDF from Yusho and Yu-Cheng patients and Canadian and Japanese populations (see Fig2).
2. for the midpoint fraction parameter (K), the value obtained by a best fit approach was $K = 100$ ng/kg bw. This is close to the *K* value determined independently from the TCDD data on rats (see Fig 1).

The liver elimination constant (k_e) was also estimated to be k_e=0.017 /week, this value provided the best general fit to the Seveso data over the time span available, according to this model.

Results

Three illustrative cases are presented here.

Case number 1. A girl, 4.4 years old at time of exposure, highly exposure.
Estimated total absorbed dose: 508750 ng TCDD or 26714 ng TCDD/kg b.w

Case number 2. A boy, 7.9 years old at time of exposure, low exposure.
Estimated total absorbed dose: 5170 ng TCDD or 216 ng TCDD/kg b.w.

Case number 3. A man, 30.2 years old at time of exposure, low exposure.
Estimated total absorbed dose: 7345 ng TCDD or 104 ng TCDD/kg b.w.

Figures no 3, 4 and 5 represent cases no1, 2 and 3 respectively, giving the projected time evolution of the body liver and adipose tissue concentrations, as well as the available data points for TCDD blood lipid concentrations.

Discussion

The fit is generally very good for the entire set of cases analysed, it tracks the evolution of adipose tissue concentration over several order of magnitudes and long time spans. It clearly shows that the effective rate of elimination varies highly as a function of body concentration, i.e. the slope on a semilog plot varies continuously. This shows clearly that the overall rate of elimination is much higher at high body burden and decreases as body burden decreases. This is true even in situations of high dilution through body growth as for the child studied in case no1. The model also predicts, that at high doses, liver concentrations are higher than those of adipose tissue, as body burden decreases the reverse becomes true. The C_h/C_{at} is always much greater than 1 immediately after a high exposure, it then decreases, at background level, this ratio is approximately 0.1 . This kinetic behaviour is similar to that observed in Yusho and Yu-Cheng patients and in animals (Carrier *et al*. 1995a,b)

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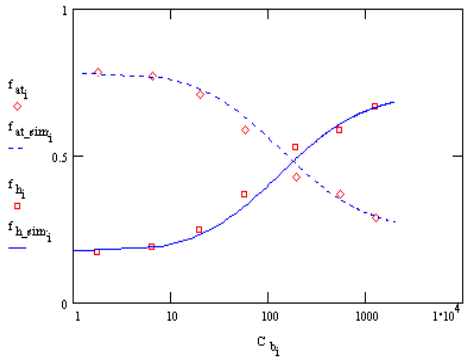


Figure 1. Observed and simulated fractions of the body burden contained in the liver and adipose tissues in rats. (Data from Abraham *et al*. (1988) measured 7 days after administation).

f_h : Fraction contained in liver (observation)
f_{h_sim} : Fraction contained in liver (simulation)
f_{at} : Fraction contained in adipose tissue (observation)
f_{at_sim} : Fraction contained in adipose tissue (simulation)
C_b : Body concentration in ng TCDD/kg bw

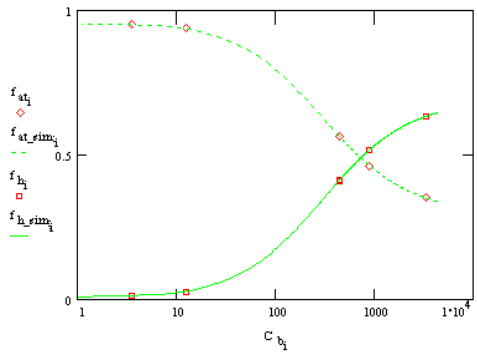
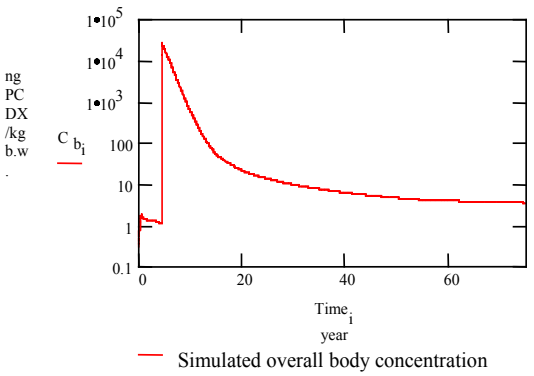


Figure 2. Observed and simulated fractions of the body burden contained in the liver and adipose tissues of 5 Yusho patients and control subjects.

(Data fram Kashimoto and Miyata (1987) and Ryan (1986))

f_h : Fraction contained in liver (observation)
f_{h_sim} : Fraction contained in liver (simulation)
f_{at} : Fraction contained in adipose tissue (observation)
f_{at_sim} : Fraction contained in adipose tissue (simulation)
C_b : Body concentration in ng 2,3,4,7,8 -PentaCDF/kg bw

Figure 3 : Case number 1
Girl, living in Zone A max, 4.4 years old at time of exposure
Estimated total absorbed dose**: 508750 ng TCDD** or **26714 ng TCDD/kg b.w.**



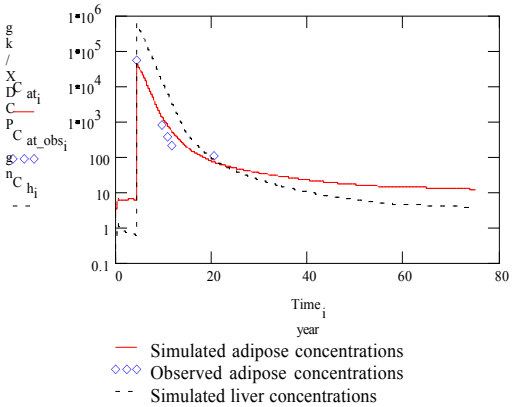


Figure 4 : Case number 2
Boy, living in Zone A min, 7.9 years old at time of exposure
Estimated total absorbed dose: **5170 ng TCDD** or **216 ng TCDD/kg b.w.**

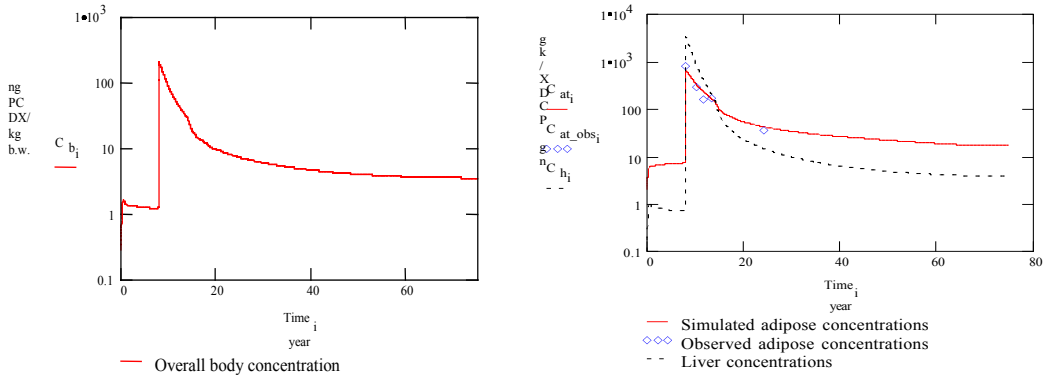


Figure 5 : Case number 3

Man, living in Zone A max, 30.2 years old at time of exposure
Estimated total absorbed dose: **7345 ng TCDD** or **104 ng TCDD/kg b.w.**