ASSESSING UNCERTAINTY IN A TOXICOKINETIC MODEL FOR HUMAN LIFETIME EXPOSURE TO TCDD

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Introduction

In 1997, the International Agency for Research on Cancer (IARC) evaluated 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as carcinogenic to humans (IARC group 1 classification) on the basis of sufficient evidence of carcinogenicity in experimental animals and limited evidence of carcinogenicity to humans[1,2]. The most important studies, which gave evidence with respect to human carcinogenicity, were four cohort studies with adequate follow-up times of herbicide producers[3,4,5,6]. There are two main reasons why occupationally exposed cohorts are such important sources of information: First, the effects are usually more pronounced because occupational exposures are higher in general, and secondly, there is improved ability to control for confounders because the workers are registered in files of companies or insurance agencies which makes necessary infomation retrieval easier and more reliable.

In the following we will focus on the so-called Boehringer cohort[6,7]. This cohort was engaged in the production of herbicides from 1950 onwards until the closing of the plant in 1984. The cohort comprised of around 1600 workers (around 25 percent females). In the plant there were 22 different working areas with different exposure to TCDD. In the 1950ies one working area seemed to have been extremely contaminated, that is, a worker faced an estimated daily TCDD exposure which exceeded the largest estimates for the other working areas for more than 20 times[7]. From 245 workers TCDD measurements from blood or body fat samples have been taken in 1985/86 and 1992-94, for some workers even multiple measurements (up to four) are available.

A central task during the risk assessment analysis of the Boehringer cohort was the backcalculation of individual TCDD concentrations from the time of measurement (1985-1994) to the period of occupation (1950-1984). This is a sensible untertaking due to the long halflife of TCDD in humans. Since cancer is a disease with a potentially long latency time, it is necessary to establish a dose-response relationship in order to link previous TCDD exposure and presently observed increase in cancer incidence. Therefore it is crucial to develop a toxicokinetic model capable of predicting TCDD concentration in human tissue during a lifetime. Such a model is useful to construct individual exposure indices like the area under the concentration-time curve (AUC). Due to the highly lipophilic nature of TCDD, and due to the fact that its distribution in the human body is a matter of weeks compared to an estimated elimination halflife of approximately 5-11 years, it is reasonable to assume a one-compartmental mass-balance equation of amount $A(t)$ of TCDD in the body at time t,

$$\mathrm{d}A(t)/\mathrm{d}t = intake(t) - elimination(t).$$

This generic model was adapted for use with the Boehringer cohort data[6,7]. Since available data did not support more complex approaches, it was assumed that the total lipid volume (TLV) of the body was constant over time and that TCDD elimination followed a simple linear kinetic, that is, $elimination(t)=k_e A(t)$. After adjusting TCDD measurements for German background exposure levels the elimination rate constant k_e was estimated from workers with multiple measurements. Working exposures in 22 different working areas were estimated by appropriately modelling the $intake(t)$-

function[6,7]. Refined analyses distinguished finally five groups of working areas with different exposure levels. These estimates were used to compute individual time courses of TCDD exposure for all cohort members, which served as basis for the further risk assessment process[6,7].

The present study focusses on two assumptions of the statistical analysis of the Boehringer cohort, that is, constant TLV over time and a simple linear elimination kinetic. Potential effects of these assumptions on the exposure estimates were investigated in a simulation study. This exercise provides valuable information on inherent uncertainties of the risk assessment approach based on backcalculated exposure matrices[8].

Methods and Materials

The simulation study was designed to mimick the essential features of the Boehringer cohort. Among others, five main working areas with different TCDD working exposure were assumed. A lognormal exposure distribution among workers was assumed with means of intake of 3500, 150, 40, 5 and 0 ng_{TCDD}/kg_{fat}/year. The highest exposure occurred only in the 1950ies. Determination of TCDD concentrations in workers happened in the early 1990ies. Mean background exposure was set to 1 ng_{TCDD}/kg_{fat}/year. Change of working area, termination of work contract, retirement and death of the virtual workers were randomly simulated as well as hiring of new workers.

The simulation study consisted of two main steps, data generation and data analysis. Data were generated according to four different scenarios (see Table 1). Data analysis always followed the analysis strategy of the Boehringer cohort as described above.

Table 1. Data generation scenarios for the simulation study.

Scenario	total lipid volume (TLV)	elimination function
I	constant over time	$k_e A(t)$ … simple
II	varying with workers age	$k_e A(t)$ … simple
III	varying with workers age	$k_{TS}[LV_{liver}(t) / TLV(t)]\, A(t)$ … according to Thomaseth and Salvan[9]
IV	varying with workers age	$k_C [f_{min} + (f_{max} - f_{min})\, C(t) / \{K + C(t)\}]\, A(t)$ … according to Carrier, Brunet and Brodeur[10,11]

The age-varying TLV values (scenarios II-IV) were randomly generated by adapting formulas and results reported by Thomaseth and Salvan[9]. These formulas also provide a basis for the elimination function of scenario III, where $LV_{liver}(t)$ denotes the lipid volume of the liver[9]. The elimination function of scenario IV is a Michaelis-Menten-type function[10,11,12], where $C(t)$ is TCDD-concentration with respect to body weight. The simulation scenarios I, II and III were replicated 100 times. The elimination function of scenario IV resulted in a computationally time-consuming procedure so that only 30 replications were performed. The SAS software system was used for statistical computations (SAS Institute Inc., Cary, NC, USA).

Results and Discussion

In Figure 1a the simulations results of working area 1 (highest exposure) are represented with boxplots. This working area only existed in the 1950ies with a mean exposure of 3500 ng_{TCDD}/kg_{fat}/year. The best results are obtained for scenario I. This is no surprise at all, since this scenario corresponds to the model assumed for data analysis. Obviously, there is a considerable amount of variation in the

simulated results, which is not surprising when TCDD are backcalculated for more than 30 years (3-5 times the halflife). If TLV is allowed to vary with age (scenarios II and III), then the bias of the obtained results will increase. However, even in the case of scenario III, where the elimination kinetic changes as well with time, the results are still acceptable at least in terms of order of magnitude. However when a Michaelis-Menten type elimination kinetic of the form of scenario IV would hold the backcalculation method used in previous risk assessment would nearly fail by an order of magnitude: the observed mean is 390 ng/kg/year which is just the ninth part of the true mean value of 3500 ng/kg/year.

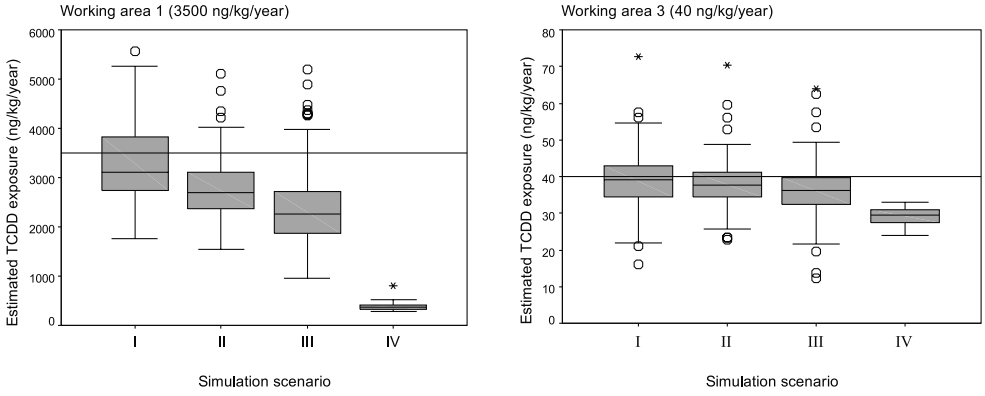

Figure 1a+b. Simulation results of estimated TCDD exposure in working area 1 (extremely high exposure only in the 1950ies) and working area 3 (medium level exposure). The horizontal lines denote the true mean exposure levels.

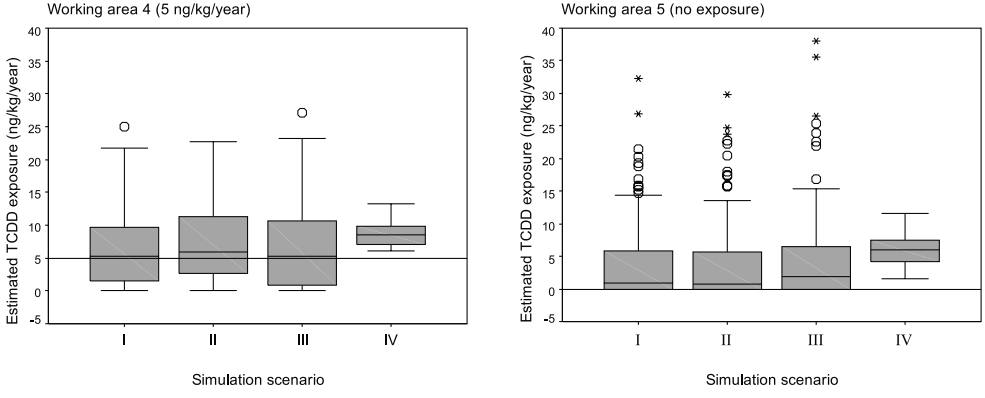

Figure 2a+b. Simulation results of working area 4 (low exposure) and 5 (no exposure). The horizontal lines denote the true mean exposure levels.

The results for working area 2 (not shown) lie in between those for working areas 1 and 3. Figure 1b shows the results for working area 3 of a medium level exposure of 40 ng/kg/year. The results for

scenarios I-III are quite satisfying here, and even under scenario IV we would get sensible results. Interestingly, the variation was much smaller in scenario IV than in I-III.

The outcomes of this simulation study are qualitatively different when considering working areas of negligible exposure. Figure 2a exhibits the results for working area 4 with a mean exposure of 5 ng_{TCDD}/kg_{fat}/year, which is just above background exposure. Still the results for scenarios I-III seem to be satisfactory on average, whereas the exposure for scenario IV is steadily overestimated now, which seems quite natural since a negative bias in the highly contaminated area has to be equalized by a positive bias in the less contaminated areas. The results obtained for the non-exposed working area 5 (Figure 2b) are interesting in two aspects. At first, overestimation for scenario IV is observed similar as in working area 4, but, secondly, around 40 percent of the estimated values for scenarios I-III are equal to the true value of zero.

The consequences of the results of our simulation study for the risk assessment process are evident. If scenarios II or III would be true, then a statistical analysis based on the assumptions of scenario I would yield biased risk estimates, but this bias would not be too bad. However, if a Michaelis-Menten-type of elimination kinetic (as in scenario IV) would be true, then the exposure indices for the highly contaminated persons would be drastically underestimated by a statistical analysis based on the assumptions of scenario I. Obviously, the knowledge of the true elimination process of TCDD in humans is crucial for a correct estimation of historical TCDD concentration using backcalculation procedures. The simulation results of our investigation reveal the possibility of an uncertainty expressing itself, both, as variation and as bias. Reduction of this uncertainty may be only possible through more valid basic knowledge about the most realistic mechanism of elimination of TCDD in humans.

Acknowledgments

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