Carrying-over Toxicokinetic Model Uncertainty into Cancer Risk Estimates: The TCDD Example

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Introduction

Estimation of human cancer risks depends on the assessment of exposure to the investigated hazardous compound as well as on its toxicokinetic and toxicodynamic in the body. Modeling these processes constitutes a basic prerequisite for any quantitative risk assessment including assessment of the uncertainty of risk estimates. Obviously, the modeling process itself is part of the risk assessment task, and it affects the development of valid risk estimates. Due to the wealth of information available on exposure and effects in humans and animals 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) provides an excellent example to elaborate methods which allow a quantitative analysis of the uncertainty of TCDD risk estimates, and which show how toxicokinetic model uncertainty carries over to risk estimate uncertainty and uncertainty of the dose-response relationship.

Cancer is usually considered as a slowly evolving disease. An increase in TCDD dose may result in an increase of the observable cancer response not until some latency time period has elapsed. This fact needs careful consideration when a dose-response relationship is to be established. Toxicokinetic models are capable to reconstruct TCDD exposure concentrations during a lifetime such that time-dependent TCDD dose metrics like the area under the concentration-time curve (AUC) can be constructed for each individual cohort member.

TCDD concentration-time curves can be obtained for individual persons by combining exposure matrices with individual residence data or, in the case of occupational exposure by using job exposure matrices and workplace data. Exposure estimates can be obtained by the back-calculation method, that is, a statistical regression model which relates TCDD measurements to the exposure matrices. Potentially rather high TCDD exposures, particularly occurring in the 1950ies, can so be reconstructed from generally lower exposures determined in the 1980 and 1990ties when TCDD concentration measurement in human body compartments became accomplishable. This reconstruction is a rather delicate task from a statistical viewpoint as an extrapolation beyond the observed range of measurements takes place. Extrapolated results cannot be verified with common model checking techniques (e.g. residual analysis). The validity of the results rises and falls with that of the underlying model assumptions.

Two potentially crucial model assumptions for estimating the exposure of a person are the assumption of lifetime constancy of total lipid volume (TLV) of the human body and the assumption of a simple linear kinetic of TCDD elimination. In 1995 a modified Michaelis-Menten kinetic (also known as Carrier kinetic) has been suggested to link the TCDD elimination rate to the available TCDD amount in the body [1,2,3]. That is, TCDD elimination would be faster, of nearly the same rate, or slower under this kinetic than under a simple linear kinetic when the individual would be highly, moderately, or slightly contaminated, respectively.

If exposure is estimated by assuming a linear elimination kinetic although a Carrier kinetic actually holds, then a compression effect will be usually observed, that is, high exposures in reality will be underestimated through statistical analysis and low exposures will be overestimated, respectively [4]. This inevitably affects the resulting individual concentration-time curves and the derived TCDD dose metric values. The present study shows how such compression effects carry over into dose-response modeling and explores the implications on the resulting risk estimates.

Methods and Materials

Occupational cohort studies produced important evidence for the evaluation of the International Agency for Research on Cancer (IARC) that TCDD is carcinogenic to humans [5,6]. One of these cohorts was the so-called Boehringer cohort comprising more than 1500 workers mainly engaged in the production of herbicides from 1950 until 1984 in Germany [7,8]. In that plant there were around 20 different working areas which could be clustered into five main areas of different TCDD exposure levels. There was e.g. one working area of the 1950ies which seemed to have been extremely contaminated, that is, those workers faced an estimated daily TCDD exposure which exceeded the largest estimates for the other working areas more than 20 times. Between 1985 and 1994 TCDD measurements from blood or body fat samples have been taken from 245 workers.

TCDD is a highly lipophilic compound which distributes fast in the human body lipids (within days or few weeks), whereas its elimination is a long lasting process (several years). These observations lead to assume a one-compartmental mass-balance equation for describing the amount $A(t)$ of TCDD in the body lipids at time t by

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

This generic model was adapted for the Boehringer cohort data [7,8]. Since available data did not support more refined approaches, it was assumed that the total lipid volume (TLV) of the body remained constant over lifetime and that TCDD elimination followed a simple linear kinetic, that is, $\mathit{elimination}(t)=k_e\,A(t)$. After adjusting TCDD measurements for German background exposure levels the elimination rate constant k_e was estimated from workers for whom multiple measurements were available. Working exposure levels in different working areas were estimated by modeling the intake function as a sum over the respective areas. The estimates of these exposure levels together with individual lifetime work history data were used to compute individual time courses of TCDD exposure for all workers of the cohort. In particular, time-dependent AUC values were used as explanatory variable in a Cox proportional hazards regression model in order to assess the effect of accumulated TCDD exposure on cancer mortality [7,8,9].

For investigating toxicokinetic model uncertainty and its effect on the risk estimates we challenged the assumptions of constant TLV and simple linear elimination kinetic. This continues previous work where we have shown that the choice of a proper TCDD elimination kinetic is crucial for the sensible reconstruction of workplace exposure levels [4].

A simulation study was designed in order to mimick the essential features of the Boehringer cohort's exposure history. Five main working areas with lognormally distributed individual TCDD exposure were assumed with mean intakes of 3500, 150, 40, 5 and 0 ng_{TCDD}/kg_{fat}/year, respectively. The highest exposure of 3500 ng_{TCDD}/kg_{fat}/year mean intake was assumed as occurred only in the 1950ies. Stop of exposure was assumed at plant closure in 1984 and determination of TCDD concentrations in cohort members was simulated to happen in the early 1990ies, when most measurements in this cohort were preformed. Mean background exposure was set to 1 ng_{TCDD}/kg_{fat}/year. Hiring, change of working area, termination of contract, retirement and death of the workers were randomly simulated. Each worker was assumed as of being under permanent hazard to develop cancer. The increase in cancer hazard was linked to TCDD exposure via the AUC dose metric. For a virtual worker diseased of cancer an increased mortality hazard was assumed and – provided still active – retirement was entailed.

Scenario	total lipid volume (TLV)	elimination function
I	Constant over time	Simple linear kinetic
II	Varying with worker's age	Simple linear kinetic
III	Varying with worker's age	Simple linear kinetic with modification according to Thomaseth and Salvan [10]
IV	Varying with worker's age	Carrier-kinetic [2,3]

Table 1. Data generation scenarios for the simulation study.

The simulation study consisted of three main steps: data generation, exposure back-calculation and dose-response modeling. Data were generated according to four different scenarios (see Table 1). The age-varying TLV values (scenarios II-IV) were randomly generated by adapting formulas and results reported by Thomaseth and Salvan [10]. These authors also provided the elimination function for scenario III. The Carrier-kinetic of scenario IV is a modified Michaelis-Menten-type function [1,2,3]. Exposure back-calculation of the simulated data was performed as it had been in the original statistical analyses of the Boehringer cohort, that is, constant TLV over time and simple linear elimination kinetic were assumed. Respectively, for the dose-response relationship of TCDD exposure on cancer mortality time-dependent AUC values were used as explanatory variable in a Cox proportional hazards regression model [7,8,9].

The simulation scenarios I, II and III were replicated 100 times each. The elimination function of scenario IV resulted in a computationally time-consuming procedure such that only 30 replications were performed. The SAS software system was used for statistical computations (SAS Institute Inc., Cary, NC, USA).

Results and Discussion

For ease of interpretation we firstly repeated the simulation results of the exposure back-calculation study, which have been presented previously [4]. Figure 1a shows the simulation results of working area 1 (highest exposure) using 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 which corresponds to the model assumed for exposure back-calculation. Obviously, there is a considerable amount of variation in the simulated results, which is not surprising when TCDD concentrations are back-calculated for more than 30 years, a period as long as 3-5 times the half-life, depending which half-life estimate is taken from the literature. Allowing TLV to vary with age (scenarios II and III) will increase the bias of the results. 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 the Carrier elimination kinetic of scenario IV would hold the back-calculation method previously used in risk assessment would nearly fail by an order of magnitude: the observed mean is 390 ng_{TCDD}/kg_{fat}/year which is just the ninth part of the true mean value of 3500 ng_{TCDD}/kg_{fat}/year.

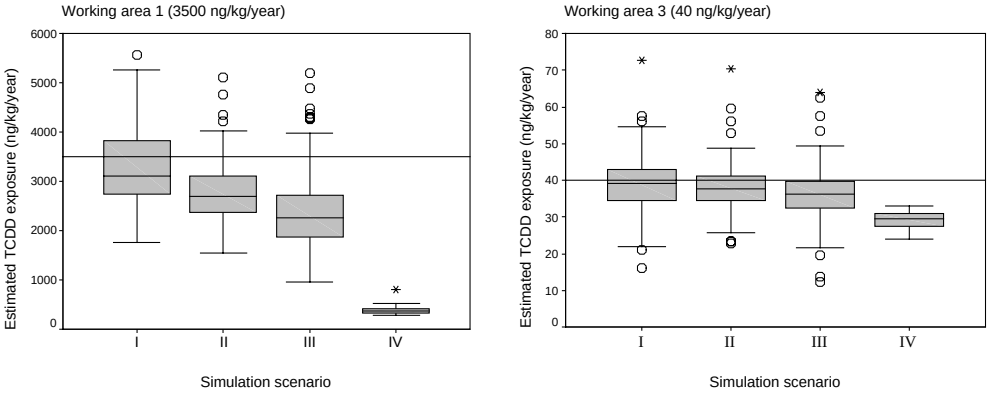

Figure 1a+b: Simulation results of estimated TCDD exposure in working area 1 (extremely high exposure only in the 1950ies) and working area 3 (medium level exposure). The horizontal lines denote the true mean exposure levels.

Figure 1b shows the results for working area 3 of a medium level exposure of 40 ng_{TCDD}/kg_{fat}/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 results for working area 2 (not shown) lie in between those for working areas 1 and 3.

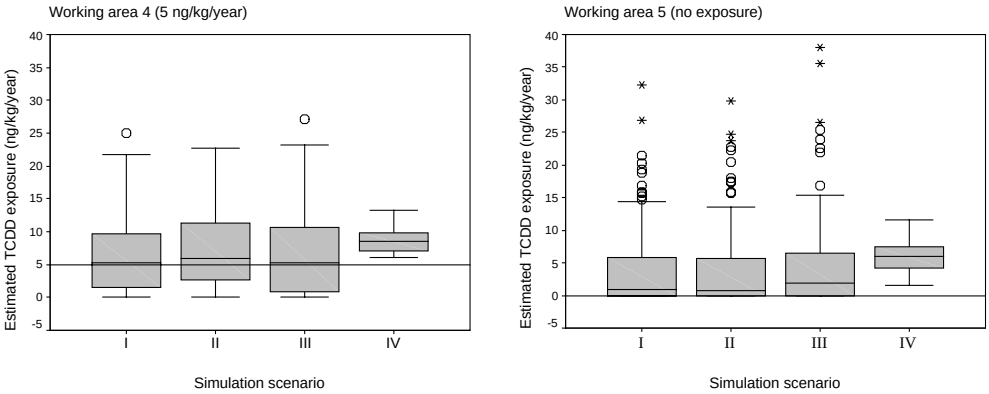

Figure 2a+b: Simulation results of working area 4 (low exposure) and 5 (no exposure). The horizontal lines denote the true mean exposure levels.

The outcomes of the 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. This 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 for working area 4. Secondly, around 40 percent of the estimated values for scenarios I-III are equal to the true value of zero as negative estimates have been set to zero.

Consequently, if scenarios II or III would be true, then a back-calculation procedure based on the assumptions of scenario I would yield biased exposure estimates, but this bias would not be too bad. However, if a Carrier elimination kinetic (as in scenario IV) would be true, then the TCDD exposure of highly contaminated workers would be drastically underestimated when back-calculation was based on the assumptions of scenario I. In contrast, the effects of minor or no exposure would be slightly overestimated. In other words, the TCDD dose metric is compressed if a linear kinetic is used to reconstruct an actually underlying Carrier kinetic.

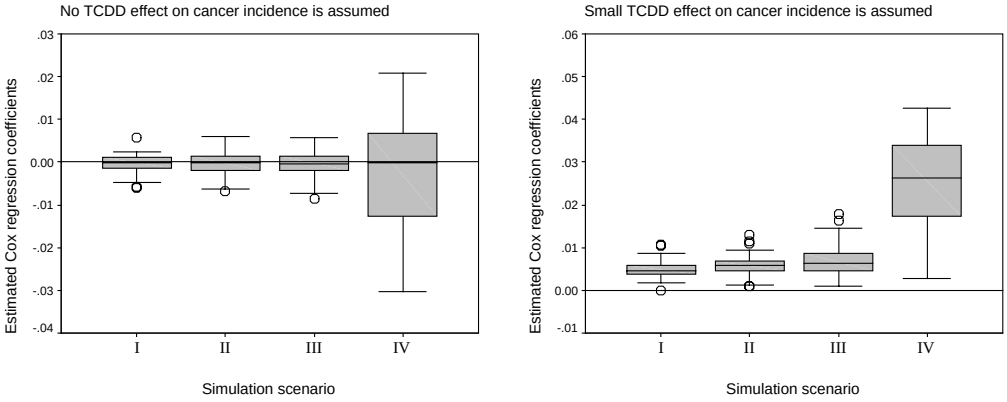

Figure 3a+b: Simulation results of relating the dose estimates derived from back-calculation to cancer mortality by employing a Cox proportional hazards regression model. No and small TCDD effects were assumed in the simulations. Positive/negative regression coefficients stand for an increase/decrease in mortality hazards, respectively. The horizontal lines at the value of 0 stand for the no TCDD effect situation which is the truth in Figure 3a. In Figure 3b the truth lies around the median of scenario I.

The impact of carrying-over the uncertainty in TCDD-dose estimates onto cancer response estimates are shown in Figures 3a and 3b. The estimated Cox regression coefficients under scenarios II and III are virtually unbiased regardless of the existence of a TCDD effect on cancer mortality. Under scenario IV (the Carrier kinetic) the variance of the estimated coefficients increases and in case of a TCDD effect a considerable bias is observed as well. Both effects are natural consequences of the TCDD dose compression seen above.

The simulation results of our investigation reveal that valid knowledge about a realistic mechanism of TCDD elimination is crucial for establishing a correct TCDD dose-cancer response relationship in humans. As long as the knowledge of the toxicokinetic and the toxicodynamic of TCDD is not fully understood any risk estimate should be considered with caution and supplied with an uncertainty analysis which takes this uncertain knowledge base into account. The simulation calculations presented above can be considered as generic for this approach and are applicable for other hazardous compounds as well.

Acknowledgments

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