

## IMPLEMENTING A CANCER RISK ASSESSMENT FOR DIOXIN USING A MARGIN OF EXPOSURE APPROACH AND AN INTERNAL MEASURE OF DOSE

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### Introduction

We recently proposed a safe exposure limit for the carcinogenic effects of tetrachlorodibenzo-*p*-dioxin (TCDD) that is based on epidemiology data, internal dose measures, and a threshold for cancer response.<sup>1</sup> The analysis included three internal dose metrics: peak, lifetime average, and integrated lifetime, or area-under-the-curve (AUC) TCDD serum level. From this analysis, we calculated safe (threshold) lifetime serum levels of TCDD (mean and lower fifth percentiles) that can be used in a margin-of-exposure analysis for calculating risks associated with exposures at a contaminated site (see table below). While we believe the concept of an internal-dose-based threshold value could become a critical element of human health risk assessments, we also acknowledge that non-traditional factors must be considered in order to properly apply the results of our analysis in a site-specific risk assessment. Specifically, as is required for assessing risks from lead exposures, a simple pharmacokinetic model is used in conjunction with site-specific scenarios to yield estimates of lifetime serum [TCDD] levels. The lifetime serum TCDD curves are then used to develop appropriate internal dose measures that can be compared with the thresholds in a margin-of-exposure analysis.

Comparison of Distribution for Background TCDD Blood Levels with Distributions for Cancer Threshold				
Total Cancer				
	Background		Threshold	
	Mean	95th %-ile	5th %-ile	Mean
AUC	158	316	617	1047
Avg	2	4	19	32
Peak	2	4	50	102

The units are serum lipid adjusted 2,3,7,8-TCDD (ppt)

This paper describes the manner in which a cancer risk assessment can be conducted using a margin-of-exposure analysis and internal dose measures. As a preliminary case study, we examine the margins of safety associated with current background TCDD exposures in the U.S.

## Methods and Materials

The kinetics of TCDD in humans are sufficiently described using a simple one-compartment pharmacokinetic model with a half-life for the elimination of TCDD of 7.5 years.<sup>2</sup> The differential equation that describes the mass balance of TCDD in the body can be coded easily into a spreadsheet. Simulations can be conducted with time-varying changes in body weight and daily dose, thus allowing any potential site-specific exposure scenario to be simulated.

The differential equation describing the time-varying changes in whole-body amount of TCDD is as follows:

$$\frac{dA(t)}{dt} = ADD - k * A$$

where A is the time-varying amount of TCDD in the body (pg/kg), ADD is the average daily dose (pg/day), k is the first-order elimination rate constant [which equals  $\ln(2)/\text{half-life}$ , =  $0.693/(7.5*365)$ , units of 1/day].

It is important to solve for the amount of TCDD in the body, rather than the concentration of TCDD, because one will want to solve for age-dependent changes in body weight (and percent lipid) when there might not be equivalent changes in dose. To solve for the concentration of TCDD, A(t) is then divided by the age-matched body weight.

Solving differential equations in a spreadsheet is simple and straightforward. The easiest method is to use the Euler's method of integration ( $A_{t=2} = A_{t=1} + dA/dt_{t=2}$ ). The calculation of the lifetime changes in TCDD levels can be conducted in six spreadsheet columns: time (days), age-dependent (and changing) daily dose, the differential equation for the rate of change in TCDD body burden, the amount of TCDD in the body, the age-dependent changes in body weight, and the concentration of TCDD in the body (lipid or non-lipid adjusted).

For the purposes of this analysis, we examine the margins of safety (threshold divided by dose) associated with "background" TCDD doses<sup>3</sup> in the U.S. of 0.1 pg TCDD/kg-day and an elevated exposure 10 times background (1.0 pg/kg-day) for a 10-year period from 20 to 30 years of age.

## Results and Discussion

Using the above values for background TCDD dose, elevated exposure, and time and age, results in lifetime serum lipid adjusted TCDD concentrations (dose measures) that yield an area under the curve (AUC) of 239 ppt-years/kg, peak concentration of 10.6 ppt, and an average lifetime TCDD level of 3.4 ppt (see Figure 1). This would result in margins of safety (a value greater than 1.0 indicates that the exposure level is less than the threshold estimate) ranging from 2.6 to 4.4, 5.6 to 9.4, and 4.7 to 9.6 for AUC, peak, and average lifetime TCDD levels, respectively (the lower end of each range is the 5<sup>th</sup> percentile divided by the respective exposed internal dose measure, and the upper end of each range is the median threshold estimate divided by the respective exposed internal dose measure). Thus, the margin of safety for this 10-year exposure at 10 times background would be between 2.6 and 9.6, depending on the dose measure and whether the central tendency or the lower 5<sup>th</sup> percentile is used as the threshold estimate.

# RISK ASSESSMENT

From Figure 1 it can be seen that longer-term exposures would yield higher estimates of all three dose metrics. This is because of the long half-life of TCDD (7.5 years) and the fact that it takes approximately 5 half-lives to reach steady state. Therefore, the margin of safety would be generally less for higher-level exposures and for longer-duration exposures.

The issue of which dose measure is the most appropriate for risk assessment purposes is open to debate. The AUC dose metric has advantages for evaluating persistent compounds<sup>2</sup>; however, other dose measures may also be useful for TCDD. The maturation of the toxicology and risk assessment disciplines has led to more advanced means of assessing risks, including the use of internal dose measures for calculating risks. For lead, a model (the integrated exposure uptake biokinetic model [IEUBK], or a physiologically based pharmacokinetic [PBPK] model<sup>4</sup>) is used to calculate the blood level of lead, and this value is compared to a safe internal blood level to assess risks for given exposure scenarios. This advancement has led to more refined estimates of exposure and risk. The understanding of the kinetics of TCDD and the risks associated with exposures has advanced to the level where a model is appropriate for use in assessing exposures (calculating internal dose measures) and risk. The methods described here are easy to apply to site-specific risk assessments and provide more advanced estimates of risk than do the older methods of assessing risks based on average daily dose.

Implementing a risk assessment using a pharmacokinetic model and internal dose measures can be accomplished easily for TCDD and related congeners. The methods outlined here could be used for each of the congeners for which congener-specific half-lives are used, and the resulting internal dose measures would be multiplied by the respective TEQs.

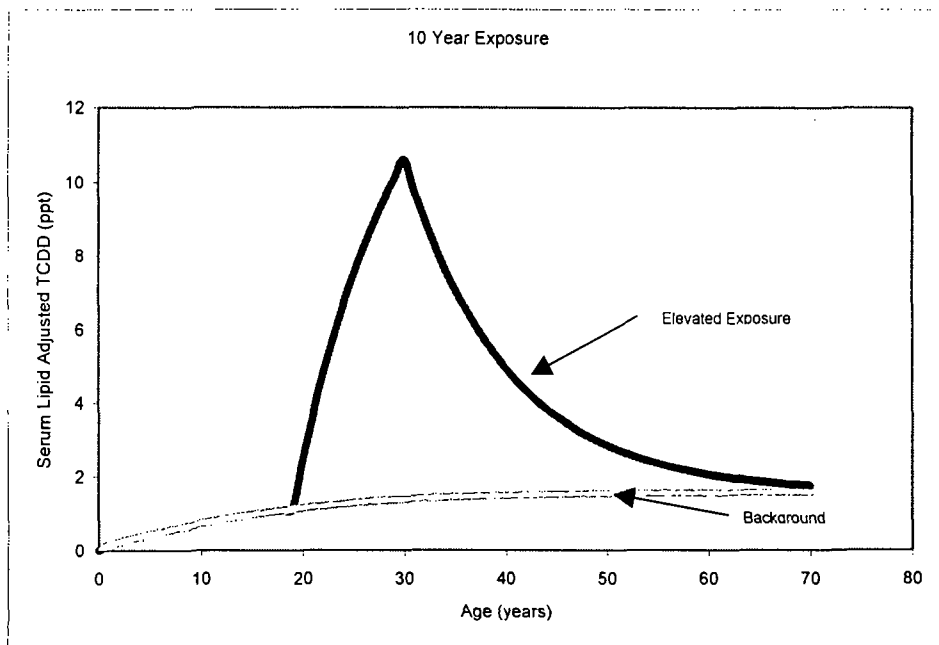


Figure 1. Lifetime reconstruction of serum lipid TCDD for background exposures and a scenario where ten times background exposures occur from the age of 20 to 30.

## References

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