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Combined Global Sensitivity Analysis and Population PBPK Modeling for Assessing Consistency of TCDD Toxicokinetics Data in Mice

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Abstract

The study of TCDD biodistribution in mice has generated a large number of data since the 1970's. The complex mechanisms involved underscores the need for a synthesis of these data. We grouped data from thirteen studies (1983-2009). A PBPK model for TCDD in mice can be calibrated based on these studies. A population PBPK approach coupled with global sensitivity analyses permitted to assess the relative contribution of each study considered as an "individual". We could also identify the key parameters that contribute at most to explain the distribution of TCDD in mice body. This identification is clearly dependent on the dose but not on the exposure route.

Keywords: 2,3,78-TCDD; Population toxicokinetics; Meta-analysis; Sensitivity analysis; Bayesian statistics.

1. Main text

Introduction

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a persistent contaminant that yields a number of adverse effects on reproduction and development due to its ability to alter hormone and receptor levels in the endocrine circuit (Birnbaum, 1994). A generalized PBPK model was developed from published PBPK models on rodents. The main compartments involved in the model were the liver, the fat, the blood, the well-perfused and the poorly-perfused tissues. The distribution, the metabolism and the excretion of TCDD were described using equations defined in Wang *et al*. (1997). Due to complex nonlinear mechanisms involved in TCDD biodistribution local sensitivity analyses may be unsuitable to fully identify the key parameters explaining TCDD kinetics. This study consequently explored the impact of the model parameters on TCDD kinetics in the framework of Global Sensitivity Analysis (GSA). Different exposure doses (low, medium and high) and routes (oral and intraperitoneal) were considered. The PBPK model was imbedded in a hierarchical population model to describe the various level of variability present in the data, according to the population toxicokinetics approach (Bois *et al*. 1996). Prior to calibration with the data,

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GSA was applied on model prediction to come up with a first subset of potential key parameters. We then defined a population distribution for these parameters and set the other ones at fixed values. After calibration with the data, GSA was used a second time to assess the consistency of the studies and identify a final set of key parameters.

Materials and Methods

Data

We compared published studies involving different strains of mice (C57BL/6N, 129/SV, CYP1A2-/-, etc.) exposed to TCDD, male and female mice, different doses (from 5pg/g BW to 25ng/g BW), different exposure routes (oral and intraperitoneal), different sampling times (from 4 hours to 42 days), and different sampled tissues (liver, brown fat, blood as specific example).

PBPK model calibration

Calibration was performed in a Bayesian framework. Prior distributions were set from the literature especially for physiological parameters. A normal distribution was assumed for the tissue concentrations and a log-linear relationship was assumed between the tissue concentrations and their corresponding variances. The latter assumption was confirmed by the data with a coefficient of determination of 94%. The PBPK model was fitted on the data with Monte Carlo Markov Chains (MCMC) methods to obtain the posterior distribution of the parameters.

Global Sensitivity Analysis and PBPK model calibration

A first sensitivity analysis was achieved on the PBPK model outputs (predicted concentrations in the liver, the fat, the well-perfused and the poorly-perfused tissues). Wide ranges of variation were used in that first analysis, especially for the chemical-specific parameters. First order and total order sensitivity indexes were calculated using the Sobol's algorithm (Sobol *et al.*, 1993). After model calibration, the consistency of the studies was assessed using the differences between the key parameters estimates at the study level and their estimates at the population level.

Results and Discussion

Physiological parameters did not have a strong impact on the predicted TCDD biodistribution. The impact of permeability coefficients rapidly decreased after 24h. Other parameters related to the distribution and the excretion also had a time-dependent sensitivity. For parameters related to the nonlinear induction of metabolism enzymes (CYP 1A2) by TCDD, the exposure doses had higher impact than the time. The most effective parameters defined at the population level were the affinities for Ah-receptors (Ahr) in the liver, the dissociation constants of the TCDD-Ahr and TCDD-Ahr-CYP1A2 complexes and the fat over blood partition coefficients. The latter parameters as well as the urinary elimination rate most distinguished the studies. Variance parameters estimates were homogenous among the studies.

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