

Modelling of the level of 1-hydroxypyrene in urine after various scenarios of dermal and inhalatory exposure to polycyclic aromatic hydrocarbons with a generic, cross-chemical predictive PBTK-model; Explanation and training exercises

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Introduction

A Physiologically Based Toxicokinetic model (PBTK) model can predict blood and urine concentrations, given a certain exposure scenario of inhalation, dermal and/or oral exposure. The recently developed PBTK-model IndusChemFate is a unified model that mimics the uptake, distribution, metabolism and elimination of a chemical in a reference human of 70 kilograms. Prediction of the uptake by inhalation is governed by pulmonary exchange to blood. Oral uptake is simulated as a bolus dose that is taken up at a first order rate. Dermal uptake is estimated by the use of a novel dermal physiologically based module that considers dermal deposition rate and duration of deposition. Moreover, evaporation during skin contact is fully accounted for and related to the volatility of the substance. Partitioning of the chemical and metabolite(s) over blood and tissues is estimated by a Quantitative Structure-Property Relationship (QSPR) algorithm. The aim of this study was to test the generic PBTK model by comparing measured urinary levels of 1-hydroxy-pyrene in various inhalation and dermal exposure scenarios with the result of model simulations.

Experimental

In the last three decades numerous biomonitoring studies of PAH-exposed humans were published that used the bioindicator 1-hydroxypyrene (1-OH-pyrene) in urine. Longitudinal studies that encompass both dosimetry and biomonitoring with repeated sampling in time were selected to test the accuracy of the PBTK-model by comparing the reported concentrations of 1-OHP in urine with the model-predicted values. Two controlled human volunteers studies and three field studies of workers exposed to Polycyclic Aromatic Hydrocarbons (PAH) were included.

Results

The urinary pyrene-metabolite levels of a controlled human inhalation study, a transdermal uptake study of bitumen fume, efficacy of respirator use in electrode paste workers, cokery workers in shale oil industry and a longitudinal study of five coke liquefaction workers were compared to the PBTK-predicted values. The simulations showed that the model-predicted concentrations of urinary pyrene and metabolites over time, as well as peak-concentrations and total excreted amount in different exposure scenarios of inhalation and transdermal exposure were in all comparisons within an order of magnitude. The model predicts that only a very small fraction is excreted in urine as parent pyrene and as free 1-OH-pyrene. The pre-dominant urinary metabolite is 1-OH-pyrene-glucuronide. Enterohepatic circulation of 1-OH-pyrene-glucuronide seems the reason of the delayed release from the body.

Conclusions

It appeared that urinary excretion of pyrene and pyrene-metabolites in humans is predictable with the PBTK-model. The model outcomes have a satisfying accuracy for early testing, in so-called *1st tier* simulations and in range finding. This newly developed generic PBTK-model IndusChemFate is a tool that can be used to do early explorations of the significance of uptake of pyrene in the human body following industrial or environmental exposure scenarios. And it can be used to optimise the sampling time and urine sampling frequency of a biomonitoring program.

At the 2012 NVvA-symposium the content of the IndusChemFate tool will be explained and training exercise will be offered (laptop needed!) – In total: 2 presentations and a training session.