High-Throughput Toxicokinetics Exposure Inference for Environmental Organic Chemicals

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Introduction

- High Throughput toxicokinetics (HTTK) methods provide the ability to characterize large numbers of chemicals by combining *in vitro* measurements and *in silico* predictions of chemical-specific TK properties with generic TK models.
- The U.S. EPA provides HTTK methods through an open-source R package “httk”, and *in vitro* bioactivity data through the ToxCast database.
- The CDC’s National Health and Nutrition Examination Survey (NHANES) provides biometric and chemical exposure biomonitoring data that are statistically representative of the U.S. population.
- Previously, reverse dosimetry was used to infer the steady-state (SS) human exposure rates for the U.S. population from urine biomonitoring data from the 2009-10 NHANES cohort for 106 environmental chemicals.
- In this project, we updated the median SS human exposure daily intake rates (mg/kg bw/day), expanding the inference to 179 parent chemicals based on NHANES biomarker data from the 2015-16 cohort with 118 exposure biomarkers.
- We extended our analysis by using two different approaches - one for semi-volatiles and non-volatiles in urine and another for volatiles in blood/plasma.
- Inference from urine was drawn using a SS assumption and a parent-metabolite stoichiometric mapping, and inference from blood for 18 volatile chemicals was made with a generic gas inhalation HTTK model.

Methods

HTTK gas inhalation PBTK model diagram

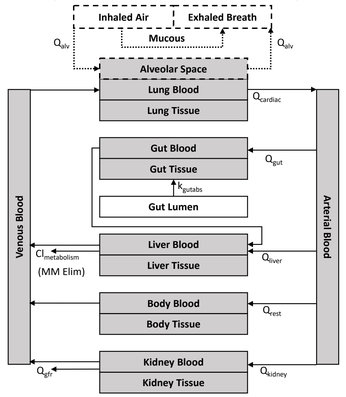

Figure 1. Representation of HTTK PBTK model structure with added gas inhalation/exhalation component (dotted lines). Gas PBTK model allows both inhalation and oral routes of exposure.

***In vitro-in vivo* extrapolation (IVIVE)**

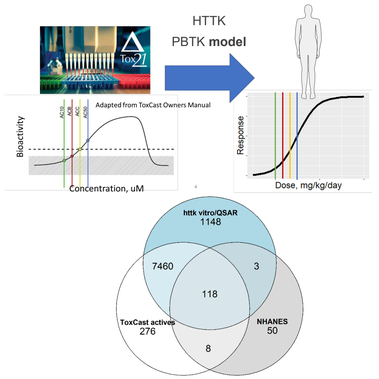

Figure 2. IVIVE is performed using HTTK PBTK model for chemicals with ToxCast AC50s and TK data in “httk”. HT chemical prioritization is performed for 118 chemicals with NHANES urine data.

High-throughput (HT) chemical risk prioritization

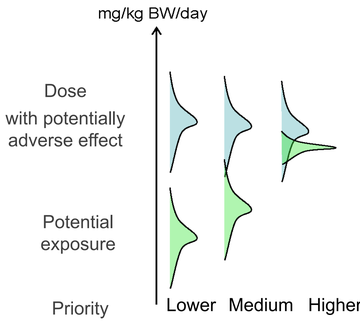

Figure 3. Evaluation of potential risk by comparing distributions of dose with potentially adverse effect and potential exposure, which are estimated by accounting for both uncertainty and variability.

Conclusions

- This update produced refined estimates of exposure, a faster workflow for integrating newly published NHANES data, and a template for analysis of other similar datasets.
- To demonstrate the importance of having the gas inhalation model, the inferences were then compared to the results from a generic oral ingestion HTTK model.
- Inclusion of volatile chemicals for high-throughput chemical risk prioritization addresses a key limitation of previous efforts.
- By placing volatile chemical risk into the context with semi- and non-volatile chemicals, priorities can be better identified.

Results

Inferred exposure for NHANES urine and blood/serum data

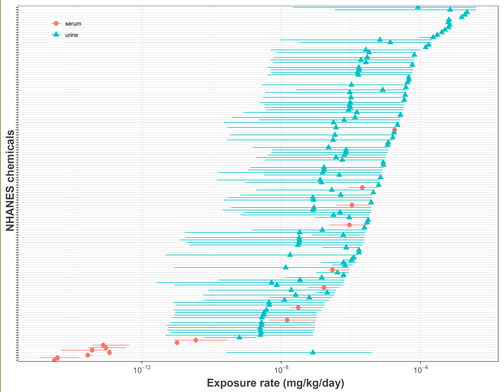

Figure 4. Population median aggregate exposures with 95% credible interval, inferred from NHANES urine biomonitoring data for 118 chemicals and NHANES blood/serum biomonitoring data for 18 chemicals. These are measured exposure data, but they can be used to evaluate models and train the Systematic Empirical Evaluation of Models (SEEM).

PBTK equivalent dose and inferred exposure for NHANES urine data

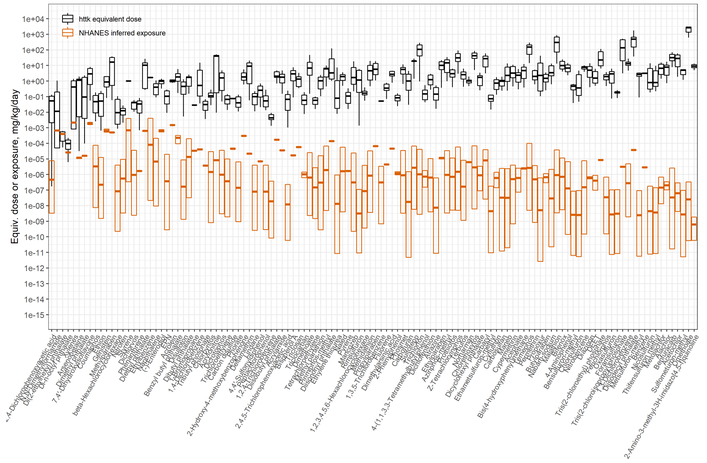

Figure 5. Comparison of equivalent doses to potential exposures for 118 environmental chemicals with NHANES urine data. The chemicals are ranked from left to right, highest to lowest priority.

GAS PBTK equivalent dose and inferred exposure for NHANES blood/serum data

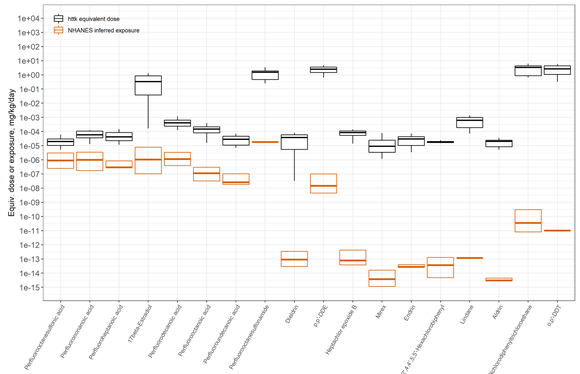

Figure 6. As a surrogate for risk we can use HTTK to convert ToxCast bioactivities into equivalent dose rates and compare the ratio of those doses to the general population exposures indicated by NHANES. Here we have used the gas inhalation PBTK model to both 1) calculate ToxCast equivalent doses for 18 environmental chemicals and 2) calculate exposure dose rates consistent with NHANES blood/serum data. The chemicals are ranked from left to right on the basis of the margin between ToxCast and NHANES, highest to lowest priority.

Comparison of HTTK generic gas inhalation and oral ingestion model inferences

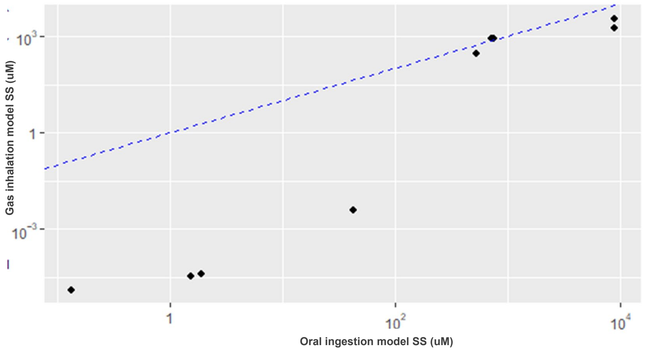

Figure 7. To calculate equivalent doses, we often use the httk prediction for steady-state plasma concentration (Css) as a function of daily oral exposure to 1 mg/kg body weight. Typically, we have considered only hepatic metabolism and kidney excretion as routes of chemical elimination. With the inhalation PBTK model we can also consider exhalation as a route of elimination. 9 out of 18 environmental chemicals examined were classified as semi-volatile chemicals by WHO guidelines using boiling points. Chemicals below the 1:1 line would have overestimated Css when exhalation is ignored.

References: Robert Pearce *et al.* (2014), Caroline Ring *et al.* (2017), Caroline Ring *et al.* (2018), John Wambaugh *et al.* (2014), Matthew Linakis *et al.* (2020), World Health Organization "Indoor air quality: organic pollutants.“ Report on a WHO Meeting (1989).