High-Throughput Toxicokinetics Exposure Inference for Environmental Chemicals

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Introduction

- High Throughput toxicokinetics (HTTK) methods provide the opportunity 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 the freely available R package "httk", and *in vitro* bioactivity data through the ToxCast database.
- The U.S. CDC conducts the National Health and Nutrition Examination Survey (NHANES), which provides biometric and chemical exposure biomonitoring data that are statistically representative of the U.S. population.
- We previously employed reverse dosimetry to infer the steady-state (SS) human exposure rates for the U.S. population from the urine biomonitoring data for the 2009-10 NHANES cohort for 106 environmental chemicals.
- Currently, we have updated the median SS human exposure daily intake rates (mg/kg bw/day), expanding the inference to 179 chemicals using new NHANES biomarker data up to the 2015-16 cohort, and performing our analysis for 118 chemicals.
- 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.
- We then used a generic gas inhalation HTTK model to further expand the number of chemical exposures inferred from NHANES blood and serum data by 18 chemicals.

Methods

HTTK gas inhalation PBTK model diagram

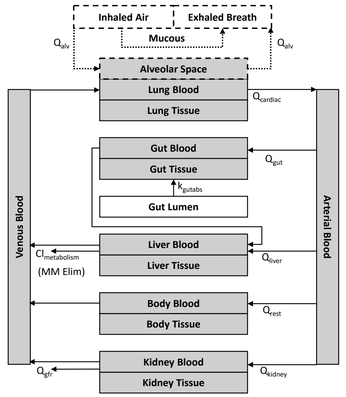

Figure 1. Representation of HTTK PBTK model structure with added gas inhalation/exhalation component (dotted lines). Gas PBTK model was used for NHANES blood and serum data.

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

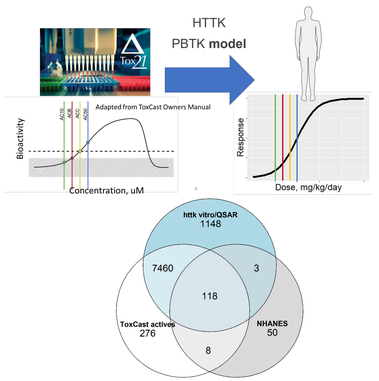

Figure 2. IVIVE is performed using HTTK PBTK model for chemicals with ToxCast AC50s and TK data in "httk". HT chemical prioritization is performed for 118 chemicals with NHANES urine data.

High-throughput (HT) chemical risk prioritization

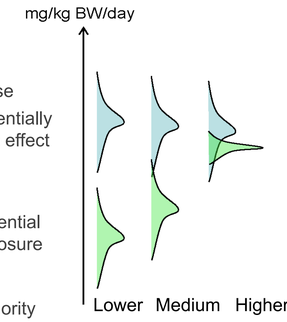

Figure 3. Evaluation of potential risk by comparing distributions of dose with potentially adverse effect and potential exposure, which are estimated by accounting for both uncertainty and variability.

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.
- Inclusion of volatile chemicals is a key improvement over previous efforts as they have previously not been addressed for high-throughput chemical risk prioritization with a Bioactivity:Exposure ratio (BER) approach.
- By placing volatile chemicals into context with semi- and non-volatile chemicals, priorities might be better identified.

Results

Inferred exposure for NHANES urine and blood/serum data

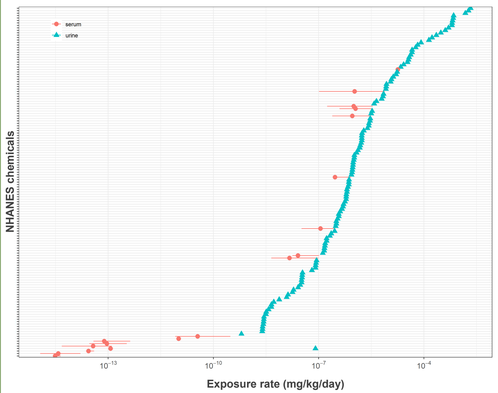

Figure 4. Population median aggregate exposures with 95% credible interval, inferred from NHANES urine biomonitoring data for 118 chemicals and NHANES blood/serum biomonitoring data for 18 chemicals. These are measured exposure data, but they can be used to evaluate models and train the Systematic Empirical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

PBTK equivalent dose and inferred exposure for NHANES urine data

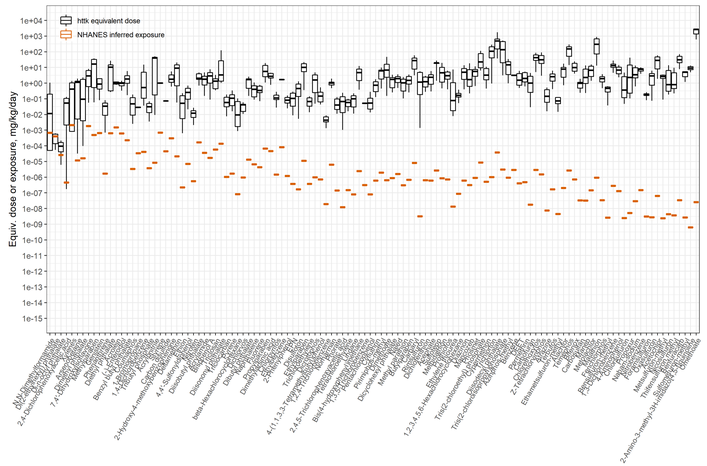

Figure 5. Comparison of equivalent doses to potential exposures for 118 environmental chemicals with NHANES urine data. The chemicals are ranked from left to right, highest to lowest priority.

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

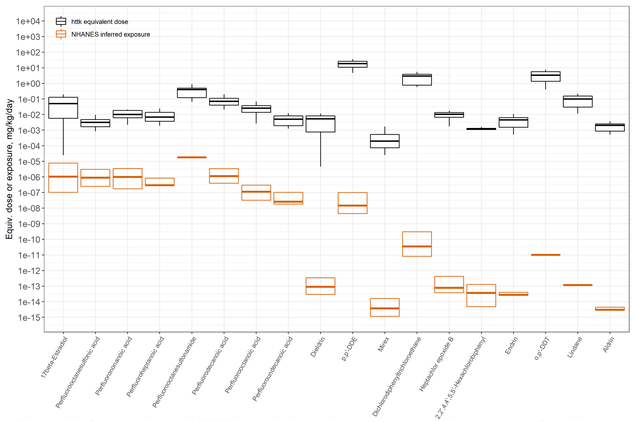

Figure 6. Comparison of PBTK equivalent doses to potential exposures for 18 environmental chemicals with NHANES blood/serum data. The chemicals are ranked from left to right, highest to lowest priority.

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

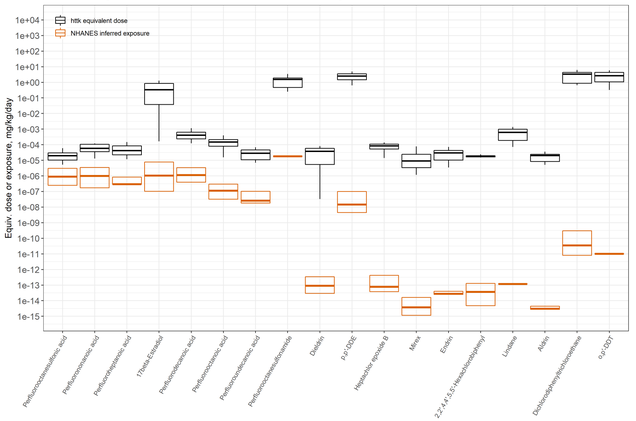

Figure 7. Comparison of GAS PBTK equivalent doses to potential exposures for 18 environmental chemicals with NHANES blood/serum data.

We can separate chemicals for semi- and non-volatiles (use left plot) and volatiles (use right plot)

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)