

Introduction

- High Throughput TK (HTTK) methods provide the ability to characterize large numbers of chemicals by combining generic TK models with *in vitro* measurements and *in silico* predictions of chemical-specific TK properties.
- 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 103 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 8 volatile chemicals was made with a generic gas inhalation HTTK model.

Methods

HTTK gas inhalation PBTK model diagram

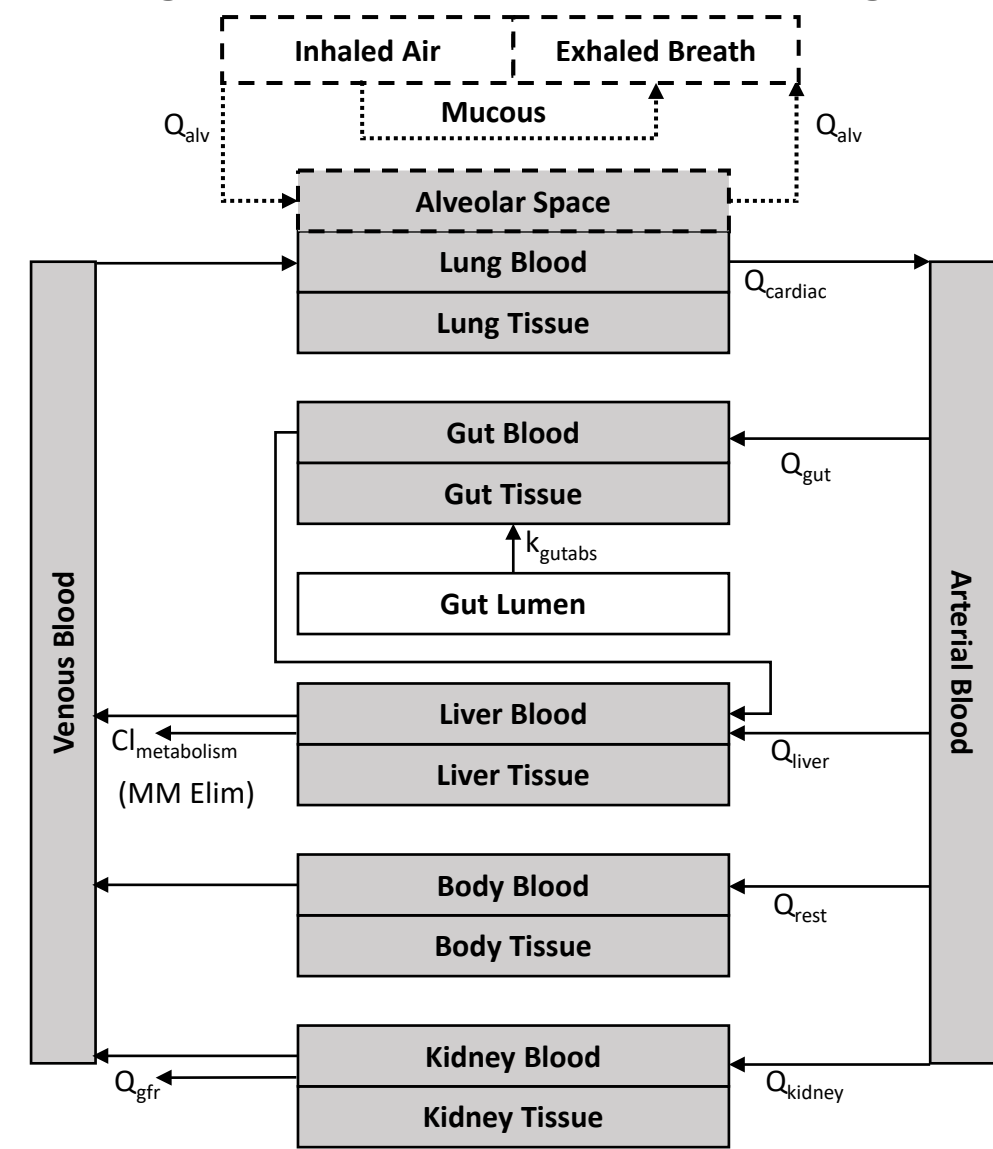


Figure 1. Representation of HTTK PBTK model structure with added gas inhalation/exhalation component (dotted lines). Gas PBTK model allows both inhalation and oral routes of exposure.

In vitro-in vivo extrapolation (IVIVE)

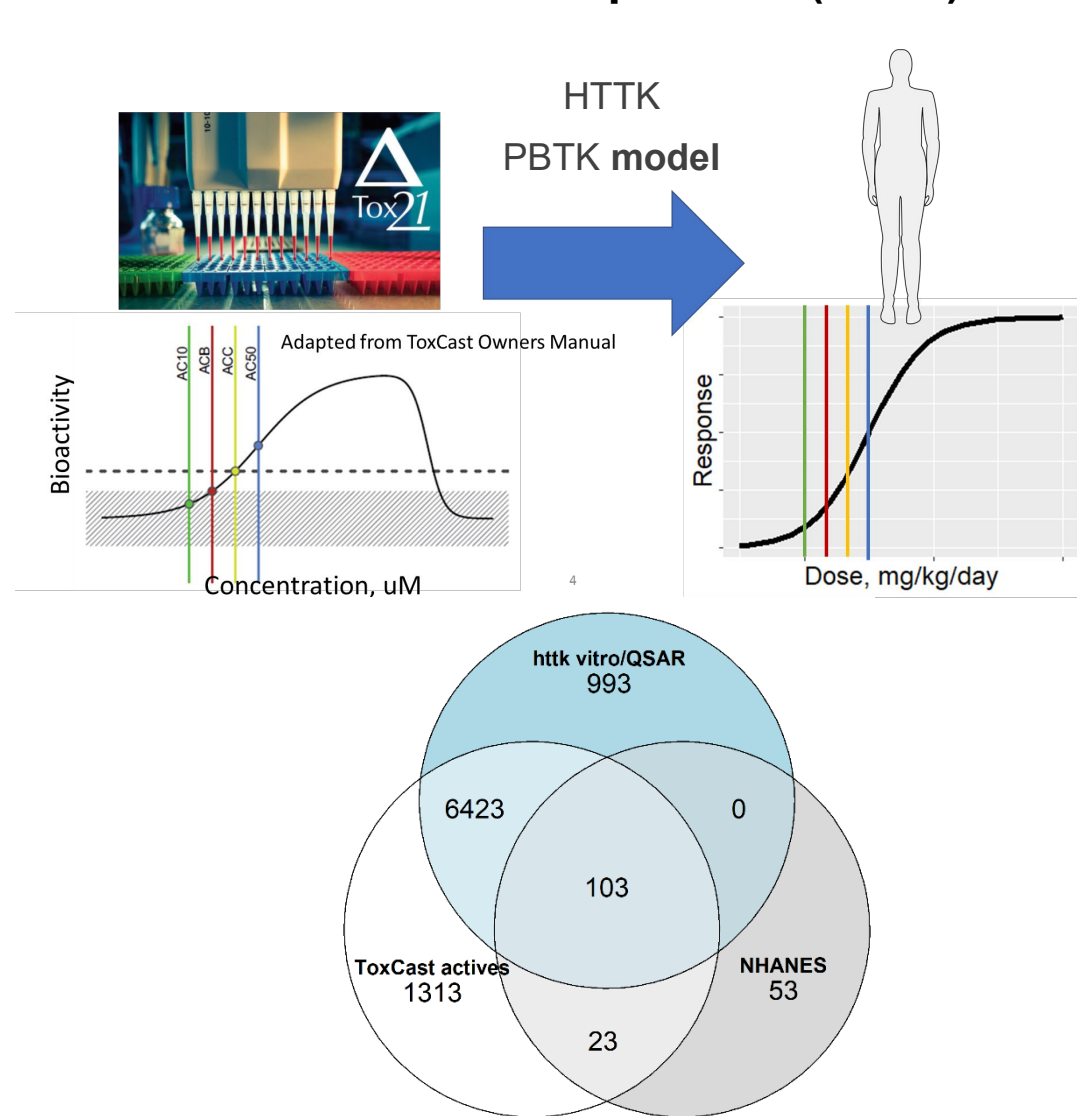


Figure 2. IVIVE is performed using HTTK PBTK model for chemicals with ToxCast AC50s and TK data in “httk”. HT chemical prioritization is performed for 103 chemicals with NHANES urine data.

High-throughput (HT) chemical risk prioritization

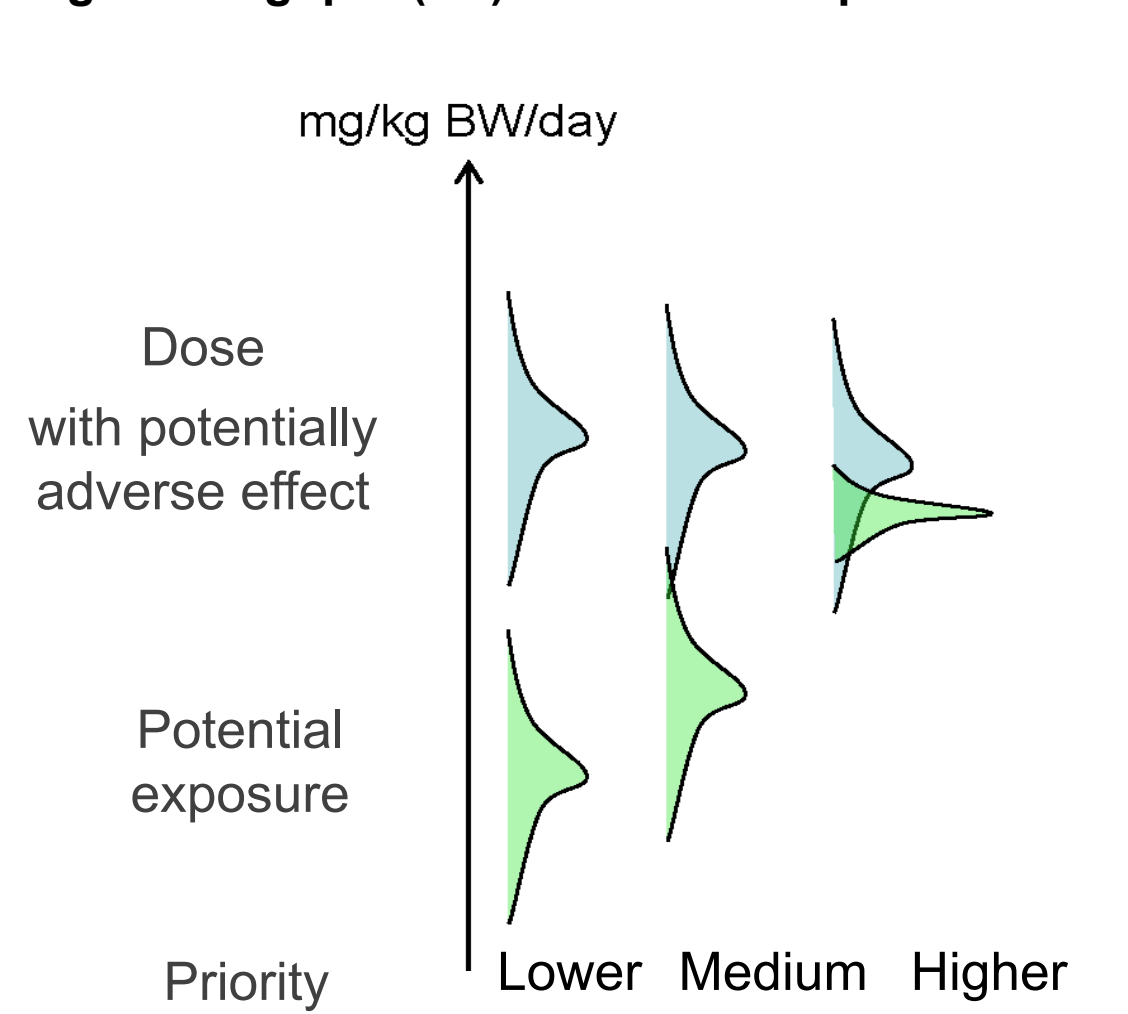


Figure 3. Evaluation of potential risk by comparing distributions of dose with potentially adverse effect and potential exposure, which are estimated by accounting for both uncertainty and variability.

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.
- Next step is to apply TK for chemicals without sufficient information to utilize HTTK methods.

Results

Inferred exposure for NHANES urine and blood/serum data

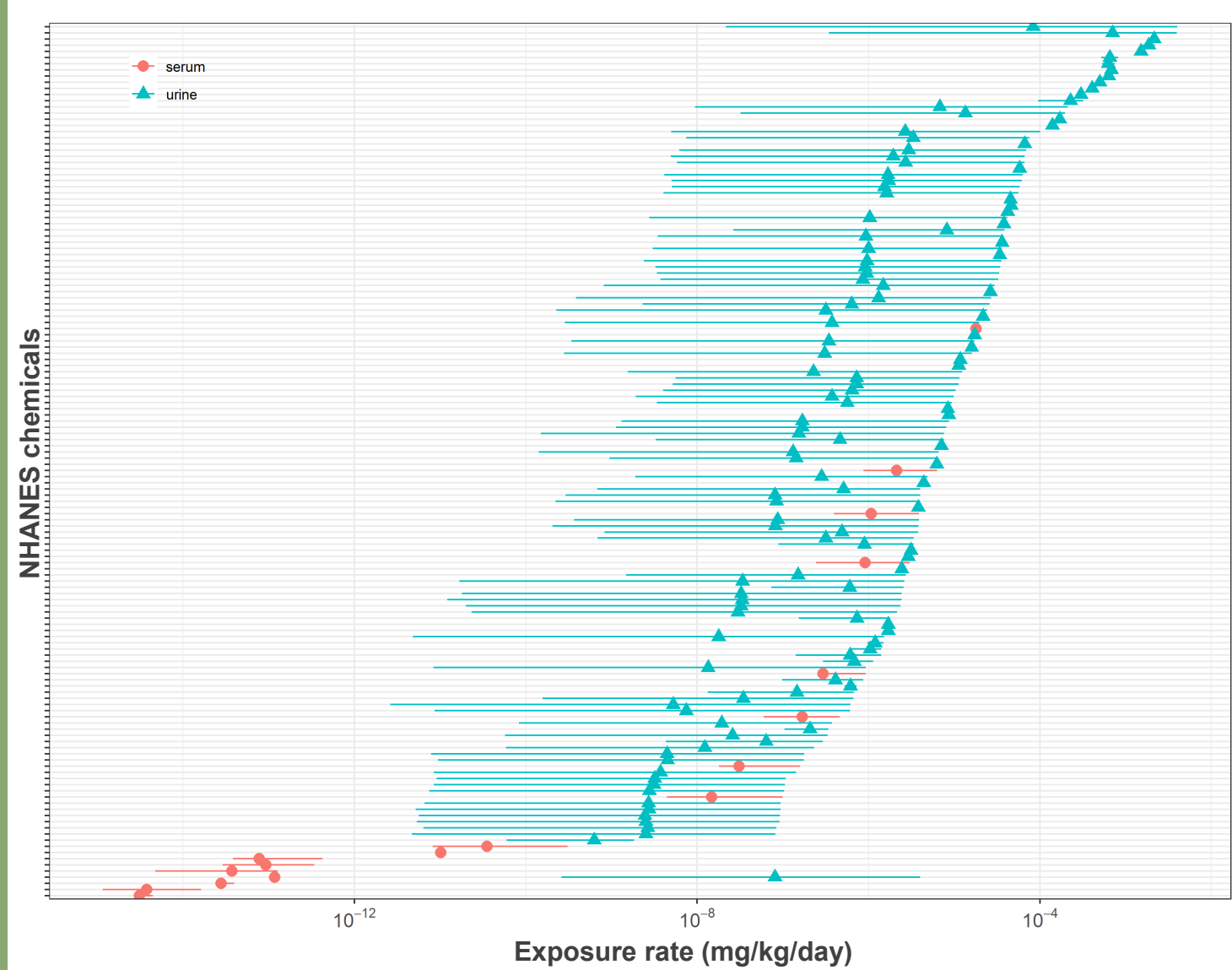


Figure 4. Population median aggregate exposures with 95% credible interval, inferred from NHANES urine biomonitoring data for 118 chemicals and NHANES blood/serum biomonitoring data for 18 chemicals. These are inferred estimates of exposure from measured data, but they can be used to evaluate models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

Ranking the chemicals from left to right, highest to lowest priority

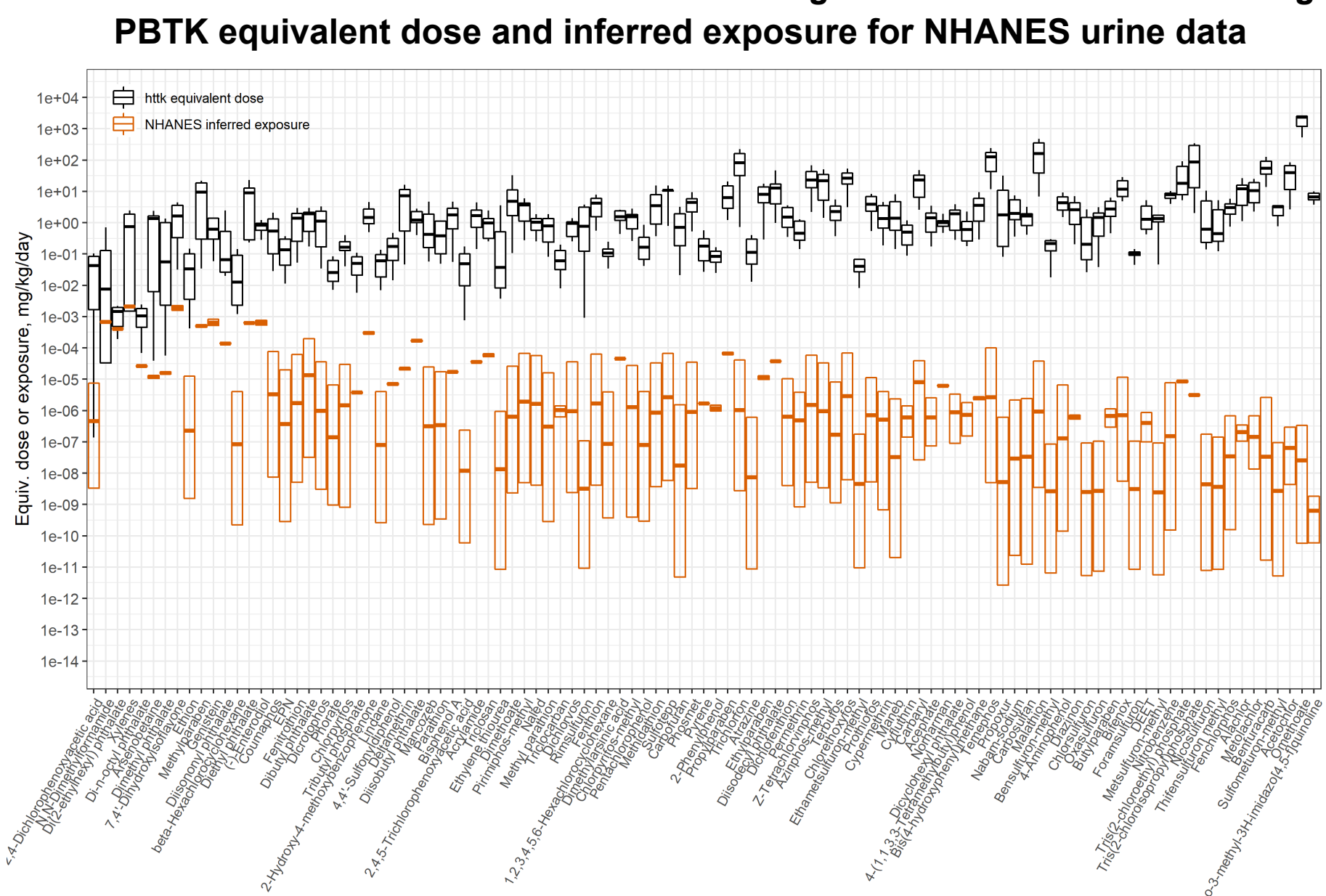


Figure 5. Comparison of equivalent doses to potential exposures for 103 environmental chemicals with NHANES urine data.

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

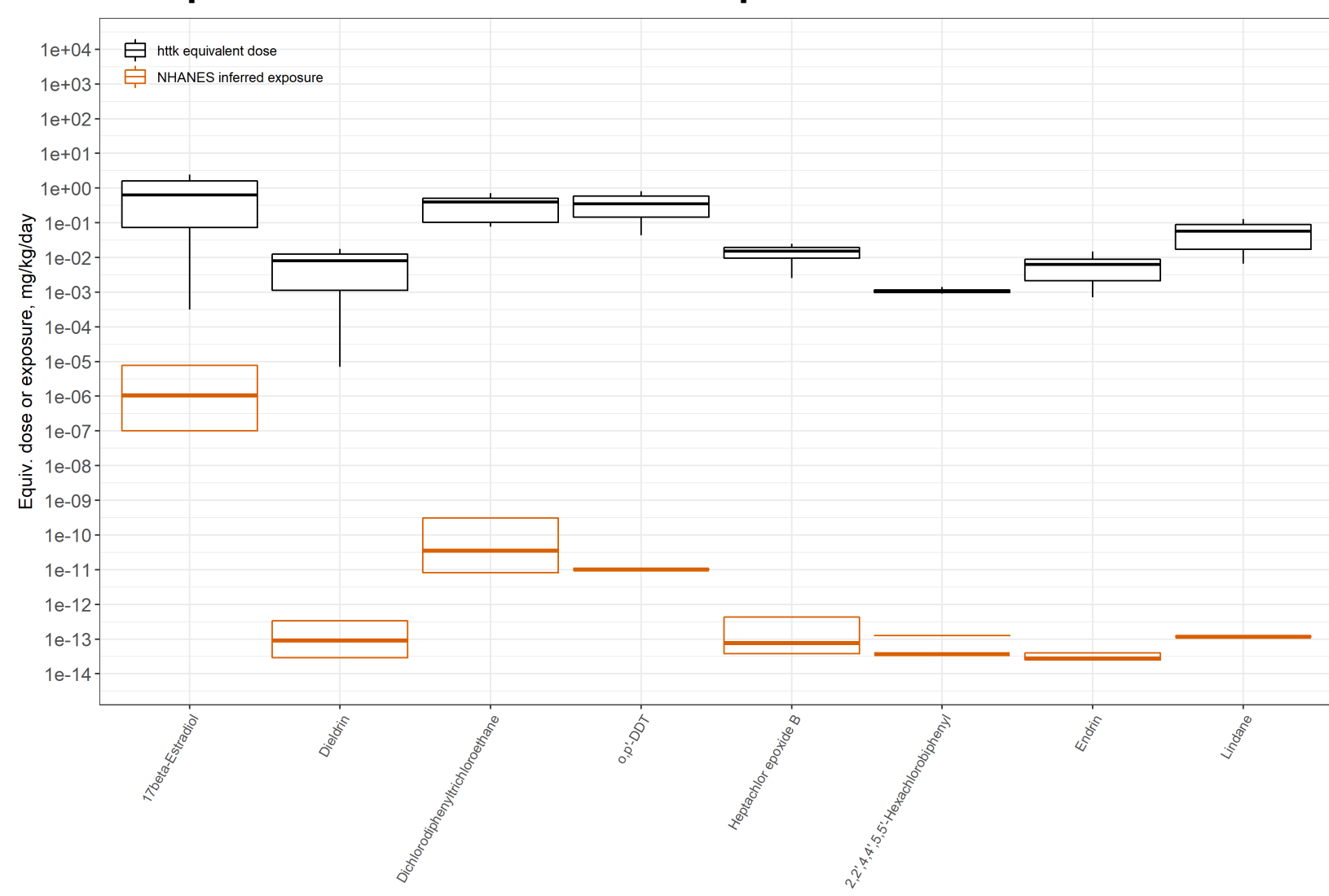


Figure 6. As a surrogate for risk we can use HTTK to convert ToxCast bioactivities into equivalent dose rates and compare the ratio of those doses to the general population exposures indicated by NHANES. Here we have used the gas inhalation PBTK model to both 1) calculate ToxCast equivalent doses for 8 environmental chemicals and 2) calculate exposure dose rates consistent with NHANES blood/serum data.

Comparison of HTTK generic gas inhalation and oral ingestion model inferences

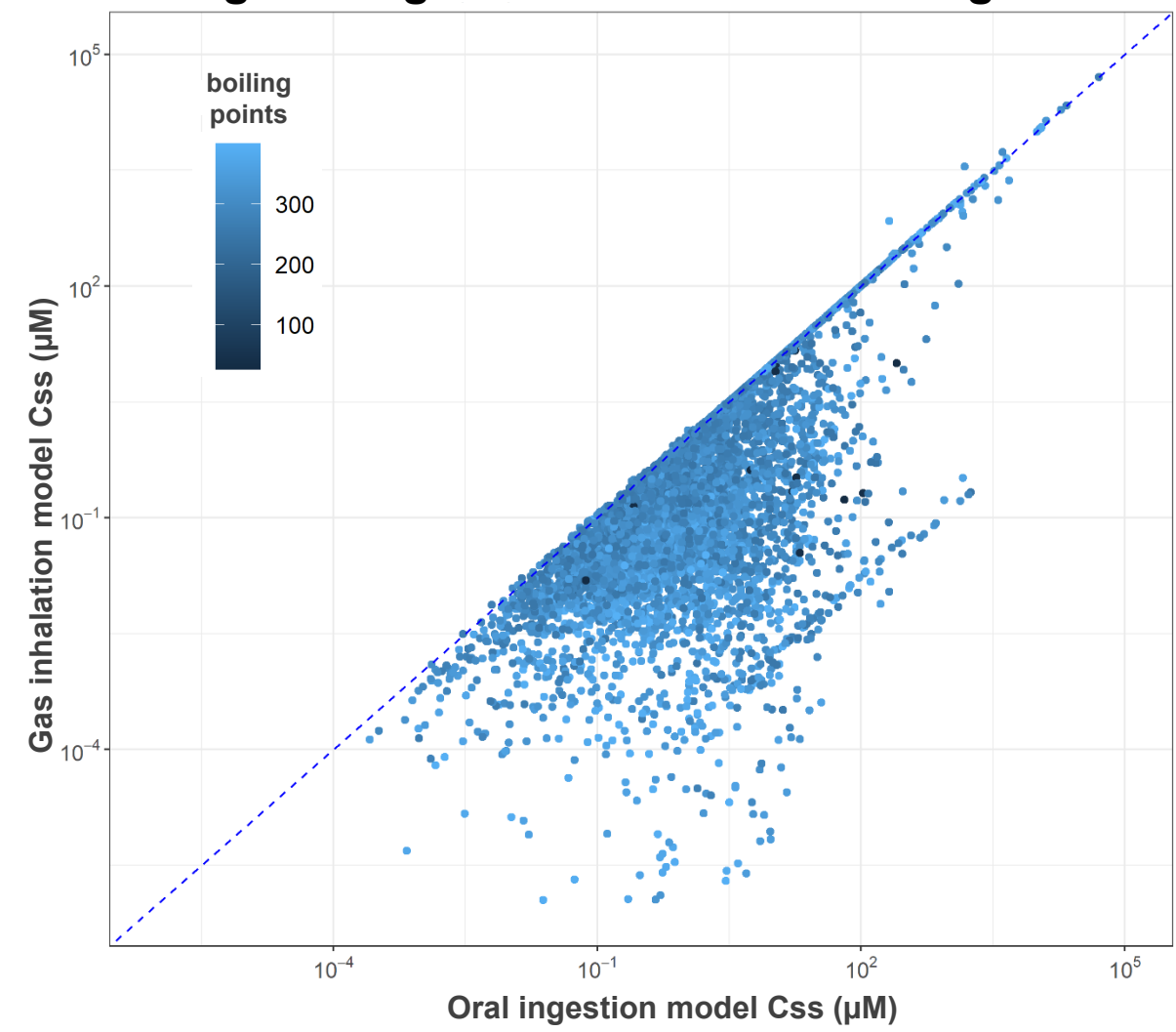


Figure 7. To calculate equivalent doses, we often use the “httk” prediction for steady-state plasma concentration (C_{ss}) as a function of daily oral exposure to 1 mg/kg body weight. Typically, we have considered only hepatic metabolism and kidney excretion as routes of chemical elimination. With the inhalation PBTK model we can also consider exhalation as a route of elimination. 5719 environmental chemicals through ToxCast database examined were classified as semi-volatile chemicals by WHO guidelines using boiling points. Chemicals below the 1:1 line would have overestimated C_{ss} when exhalation is ignored.