High-Throughput Toxicokinetics Inhalation Exposure Inferences for Organic Chemicals

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Introduction

- The National Health and Nutrition Examination Survey (NHANES) provides biometric and chemical exposure biomonitoring data that are statistically representative of the modern U.S. population.
- High-throughput toxicokinetics (HTTK) R package is open-source software which includes several toxicological models and supporting data.
- We are working to update the chemical exposure rates that can be inferred from the NHANES biomonitoring data. Previously these inferences included only semi-volatile and non-volatile chemicals. Here, we are developing methods for volatile chemicals.
- HTTK-pop Monte Carlo (MC) simulator draws from the NHANES biometrics to simulate toxicokinetic variability but utilizes data only up to the 2011-12 NHANES cohort.
- We updated HTTK-pop MC by obtaining the most recently available NHANES biometrics, up to the 2017-18 NHANES cohort.
- We examined steady-state human exposure rates for the median and upper 95th percentile of the U.S. population inferred using reverse dosimetry from the NHANES chemical exposure biomarker data in blood and plasma.
- We also expanded the HTTK reverse dosimetry beyond oral exposures using the recently added generic inhalation Physiologically Based Toxicokinetic (PBTK) model by finding a steady-state solution.

HTTK Inhalation Model Plasma Steady-State Solution

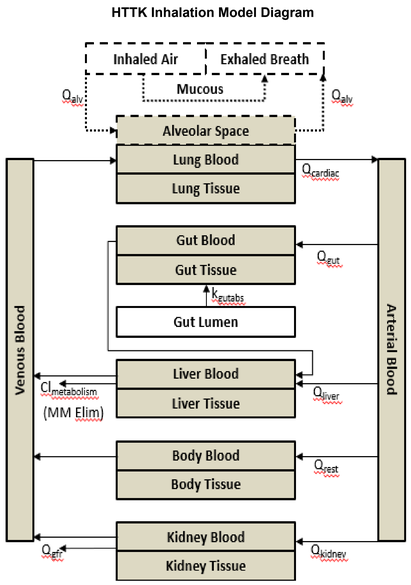

Figure 1. Representation of HTTK PBTK model structure with added gas inhalation/exhalation component (dotted lines). Blood flow rates represented with *Q*, tissue compartments and associated blood supplies represented with rectangles. Some chemical is cleared from the system through liver metabolism and glomerular filtration.

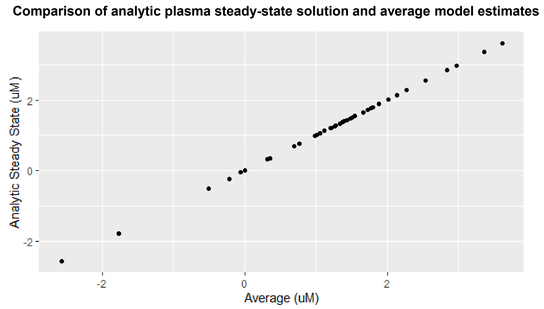

Figure 2. Log-transformed plasma analytic steady-state solution vs. average model estimates for 41 chemicals.

Analytic Steady-State Solution for Plasma Concentration: Css_ven / Rblood2plasma

```
Css_ven = Cinh*Rblood2air*(kUrt*Qgfr*Qgut^2*fup + 2*kUrt*Qgfr*Qgut*Qliver*fup + kUrt*Qgfr*Qgut*Qlung*fup +
kUrt*Qgfr*Qgut*Qrest*fup + kUrt*Qgfr*Qliver^2*fup + kUrt*Qgfr*Qliver*Qlung*fup +
kUrt*Qgfr*Qliver*Qrest*fup + kUrt*Qgfr*Qlung*fup*Clmetabolism + kUrt*Qgfr*Qrest*fup*Clmetabolism +
kUrt*Qgut^2*Qkidney*Rblood2plasma + kUrt*Qgut*Qkidney^2*Rblood2plasma +
2*kUrt*Qgut*Qkidney*Qliver*Rblood2plasma + kUrt*Qgut*Qkidney*Qlung*Rblood2plasma +
kUrt*Qgut*Qkidney*Qrest*Rblood2plasma + kUrt*Qkidney^2*Qliver*Rblood2plasma +
kUrt*Qkidney^2*Clmetabolism*Rblood2plasma + kUrt*Qkidney*Qliver^2*Rblood2plasma +
kUrt*Qkidney*Qliver*Qlung*Rblood2plasma + kUrt*Qkidney*Qliver*Qrest*Rblood2plasma +
kUrt*Qkidney*Qlung*Clmetabolism*Rblood2plasma + kUrt*Qkidney*Qrest*Clmetabolism*Rblood2plasma -
2*Qalv*Qgfr*Qgut^2*fup - 4*Qalv*Qgfr*Qgut*Qliver*fup - 2*Qalv*Qgfr*Qgut*Qlung*fup -
2*Qalv*Qgfr*Qgut*Qrest*fup - 2*Qalv*Qgfr*Qliver^2*fup - 2*Qalv*Qgfr*Qliver*Qlung*fup -
2*Qalv*Qgfr*Qliver*Qrest*fup - 2*Qalv*Qgfr*Qlung*fup*Clmetabolism - 2*Qalv*Qgfr*Qrest*fup*Clmetabolism -
2*Qalv*Qgut^2*Qkidney*Rblood2plasma - 2*Qalv*Qgut*Qkidney^2*Rblood2plasma -
4*Qalv*Qgut*Qkidney*Qliver*Rblood2plasma - 2*Qalv*Qgut*Qkidney*Qlung*Rblood2plasma -
2*Qalv*Qgut*Qkidney*Qrest*Rblood2plasma - 2*Qalv*Qkidney^2*Qliver*Rblood2plasma -
2*Qalv*Qkidney^2*Clmetabolism*Rblood2plasma - 2*Qalv*Qkidney*Qliver^2*Rblood2plasma -
2*Qalv*Qkidney*Qliver*Qlung*Rblood2plasma - 2*Qalv*Qkidney*Qliver*Qrest*Rblood2plasma -
2*Qalv*Qkidney*Qlung*Clmetabolism*Rblood2plasma -
2*Qalv*Qkidney*Qrest*Clmetabolism*Rblood2plasma)/((2*Qgfr*Qgut^2*fup*Kblood2air +
4*Qgfr*Qgut*Qliver*fup*Kblood2air + 2*Qgfr*Qgut*Qlung*fup*Kblood2air + 2*Qgfr*Qgut*Qrest*fup*Kblood2air -
2*Qgfr*Qgut*fup*Kblood2air*Qcardiac + 2*Qgfr*Qliver^2*fup*Kblood2air + 2*Qgfr*Qliver*Qlung*fup*Kblood2air
+ 2*Qgfr*Qliver*Qrest*fup*Kblood2air - 2*Qgfr*Qliver*fup*Kblood2air*Qcardiac +
2*Qgfr*Qlung*fup*Clmetabolism*Kblood2air + 2*Qgfr*Qrest*fup*Clmetabolism*Kblood2air -
2*Qgfr*fup*Clmetabolism*Kblood2air*Qcardiac + 2*Qgut^2*Qkidney*Rblood2air*Rblood2plasma +
2*Qgut*Qkidney^2*Kblood2air*Rblood2plasma + 4*Qgut*Qkidney*Qliver*Kblood2air*Rblood2plasma +
2*Qgut*Qkidney*Qlung*Kblood2air*Rblood2plasma + 2*Qgut*Qkidney*Qrest*Kblood2air*Rblood2plasma -
2*Qgut*Qkidney*Kblood2air*Qcardiac*Rblood2plasma + 2*Qkidney^2*Qliver*Kblood2air*Rblood2plasma +
2*Qkidney^2*Clmetabolism*Kblood2air*Rblood2plasma + 2*Qkidney*Qliver^2*Kblood2air*Rblood2plasma +
2*Qkidney*Qliver*Qlung*Kblood2air*Rblood2plasma + 2*Qkidney*Qliver*Qrest*Kblood2air*Rblood2plasma -
2*Qkidney*Qliver*Kblood2air*Qcardiac*Rblood2plasma + 2*Qkidney*Qlung*Clmetabolism*Kblood2air*Rblood2plasma
+ 2*Qkidney*Qrest*Clmetabolism*Kblood2air*Rblood2plasma -
2*Qkidney*Clmetabolism*Kblood2air*Qcardiac*Rblood2plasma + kUrt*Qgfr*Qgut*fup + kUrt*Qgfr*Qliver*fup +
kUrt*Qgfr*fup*Clmetabolism + kUrt*Qgut*Qkidney*Rblood2plasma + kUrt*Qkidney*Qliver*Rblood2plasma +
kUrt*Qkidney*Clmetabolism*Rblood2plasma - 2*Qalv*Qgfr*Qgut*fup - 2*Qalv*Qgfr*Qliver*fup -
2*Qalv*Qgfr*fup*Clmetabolism - 2*Qalv*Qgut*Qkidney*Rblood2plasma - 2*Qalv*Qkidney*Qliver*Rblood2plasma -
2*Qalv*Qkidney*Clmetabolism*Rblood2plasma)*Qcardiac)
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The HTTK-pop MC human variability simulator (Ring et al., 2017) uses a steady-state solution to a PBPK model to allow MC simulation. In this case, we had to derive a new steady-state solution for the Linakis et al. (2020) HTTK inhalation PBTK model.

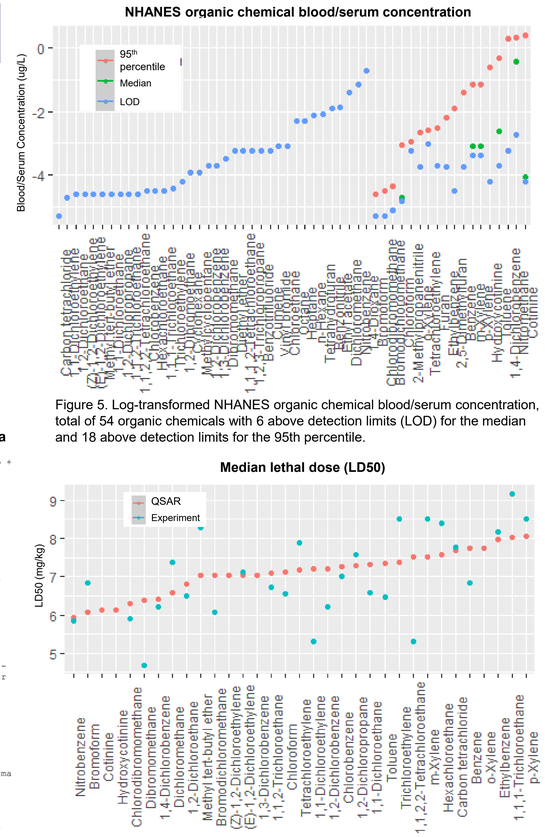

Figure 5. Log-transformed NHANES organic chemical blood/serum concentration, total of 54 organic chemicals with 6 above detection limits (LOD) for the median and 18 above detection limits for the 95th percentile.

Figure 6. Log-transformed LD50 with NHANES organic chemical blood/serum concentration data. LD50 value was obtained for 33 chemicals from T.E.S.T QSAR LD50 prediction and 28 chemicals from ChemIDplus experimental data.

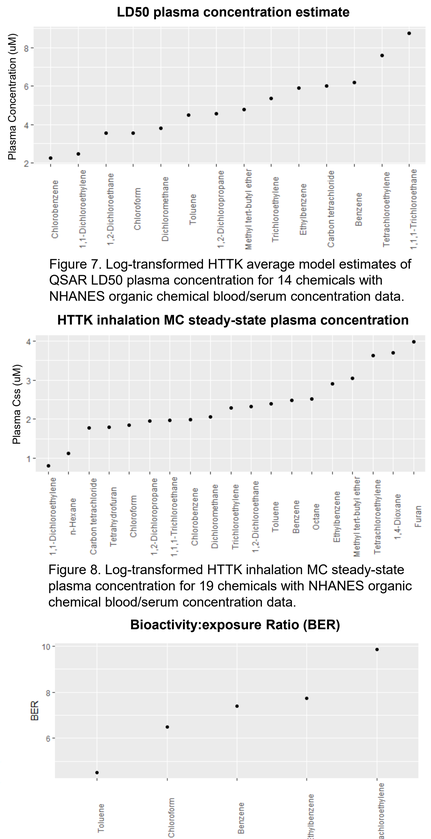

Figure 7. Log-transformed HTTK average model estimates of QSAR LD50 plasma concentration for 14 chemicals with NHANES organic chemical blood/serum concentration data.

Figure 8. Log-transformed HTTK inhalation MC steady-state plasma concentration for 19 chemicals with NHANES organic chemical blood/serum concentration data.

Figure 9. Log-transformed bioactivity:exposure ratio for 5 chemicals with NHANES organic chemical blood/serum concentration data using 95th percentile.

Results

NHANES biometrics and HTTK-pop MC simulator

	Total		Male		Female		Adults		Youth	
Weight (kg)	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean
NHANES 2007-2012	67.6	64.2	73	67.5	63	60.9	79	82	30.8	37.7
NHANES 2013-2018	67.8	65.2	72.9	68.2	63.5	62.4	79.2	82.7	32.2	38.8
Height (cm)	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean
NHANES 2007-2012	163	158	171	162	159	153	167	168	143	140
NHANES 2013-2018	162	157	170	162	158	153	166	167	144	140

Table 1. Comparison of mean/median weight and height of the previous cohort (2007-12 NHANES cohort) and updated cohort (2013-18 NHANES cohort) for five subgroups: Total, Male, Female, Adults (age 20+ years old), and Youth (age 2-19 years old).

The HTTK-pop MC human variability simulator replicates the correlation structure indicated by the NHANES.

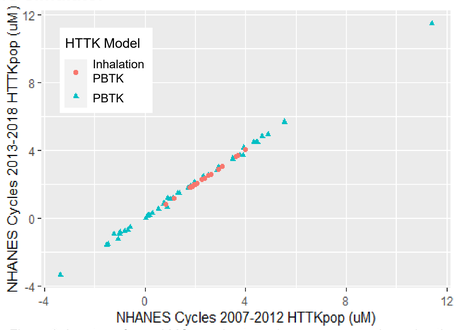

Figure 3. Log-transformed MC steady-state plasma concentration using the previous cohort (2007-12 NHANES cohort) versus updated cohort (2013-18 NHANES cohort) for 19 chemicals with the HTTK inhalation PBTK model and 44 chemicals with the HTTK PBTK model.

NHANES organic chemical half-life

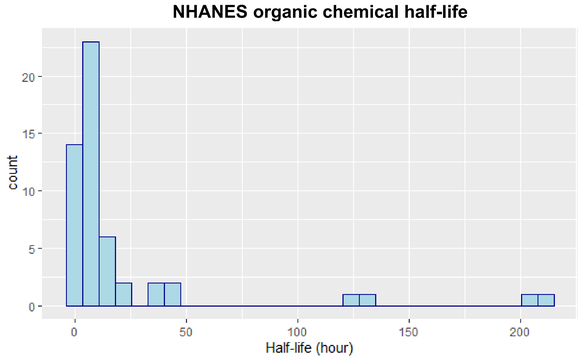

Figure 4. Histogram of QSAR model estimated elimination half-life for 52 chemicals. We had one outlier with half-live of 6793.24 hour (Hexachloroethane) which was omitted in the histogram.

Conclusions

- Comparison of previous cohort (2007-12 NHANES cohort) and updated cohort (2013-18 NHANES cohort) indicates some increase in mean and median body weights for the updated cohort with no change or a slight decrease in body heights.
- Inclusion of volatile chemicals is a key improvement over previous efforts as they have previously not been addressed with a BER approach.
- By placing volatile chemicals into context with semi- and non-volatile chemicals, priorities might be better identified.

References

1) Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017a): 1.
2) Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment international 106 (2017): 105-118.
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4) Linakis, Matthew W., et al. Development and evaluation of a high throughput inhalation model for organic chemicals." *J Expo Sci Environ Epidemiol.* (2020): DOI: 10.1038/s41370-020-0248-9.
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