INFERRING POPULATION EXPOSURE FROM BIOMONITORING DATA ON URINE CONCENTRATIONS ABSTRACT # 2234n

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ABSTRACT

Biomonitoring studies such as the National Health and Nutrition Examination Survey (NHANES) are valuable to exposure assessment both as sources of data to evaluate exposure models and as training sets to develop heuristics for rapid-exposure-assessment tools. However, linking individual measurements of urine concentrations of a metabolite back to an individual's exposure rate is generally difficult, because: urine concentrations need to be converted to excretion rates; parent chemical exposures are inferred from multiple, sometimes overlapping metabolites measured in urine; and the same observation may be due to a less-recent, large exposure or a more-recent, smaller exposure. While individual measures are problematic, we demonstrate approaches to solutions for the above problems for population distributions of exposure. We calibrate models for gender-, ethnicity-, age-, and bodyweight-dependent predictors of creatinine production rate for the US population, based on the 2009-2010 NHANES sample. We use Bayesian methods to infer parental exposure given measurements on metabolites, allowing for the fact that multiple parents may yield the same metabolite. We show results of simulations with stochastic exposure scenarios that demonstrate that simple models assuming steady-state exposure give approximately the correct population median, but that the population variance of exposure depends on the exposure variance, the frequency of exposure events, and aspects of pharmacokinetics, and is thus is more problematic. However, the population variance can be bounded, and even uncertain knowledge of pharmacokinetics can help improve exposure estimates.

INTRODUCTION

The National Health and Nutrition Examination Survey (NHANES) is a repeating survey of health-related characteristics of the US population. The sample is based on a design targeted at getting estimates that validly represent the whole population.

Our goal is to use the biomonitoring data from NHANES to develop estimates of exposures to environmental chemicals, for use in evaluating models that predict exposure.

Both serum and urine are evaluated for exogenous chemicals in select individuals. Here, we discuss issues surrounding evaluating urine samples.

This poster discusses our approach to solving three problems:

- Mostly it is metabolites of chemicals of interest that are measured in urine, but we want to track those measurements back to exposure to the parent chemicals, where the relationship between metabolite and parent is often not 1:1.
- NHANES urinary concentration data are measured per urine volume and per mg creatinine. Before 2009, the relevant volume of urine was not reported. We use the 2009-2010 data to develop a model for daily creatinine excretion rates that depend on age, weight, gender, and ethnicity/race.
- Models to extrapolate back to exposure rates need to make some simplifying assumptions, particularly that exposure is analogous to a constant infusion. The reality is more complex - even in the absence of pharmacokinetic and exposure variability, the mechanics of how exposures occur generate variability in urinary measures. How well can we estimate population mean exposures under the steady-state exposure assumption?

A PREDICTOR for CREATININE EXCRETION RATE

Data were taken directly from SAS xport files for the 2009-2010 cycle of NHANES. Daily creatinine excretion (CER) is extrapolated from urinary creatinine concentration and the volume and time since last void for the urine samples taken as part of the NHANES lab visit for NHANES participants.

The analysis was carried out using the R statistical programming environment (R-core, 2013), and takes the sampling design into account, using the package "survey" (Lumley 2004, 2012).

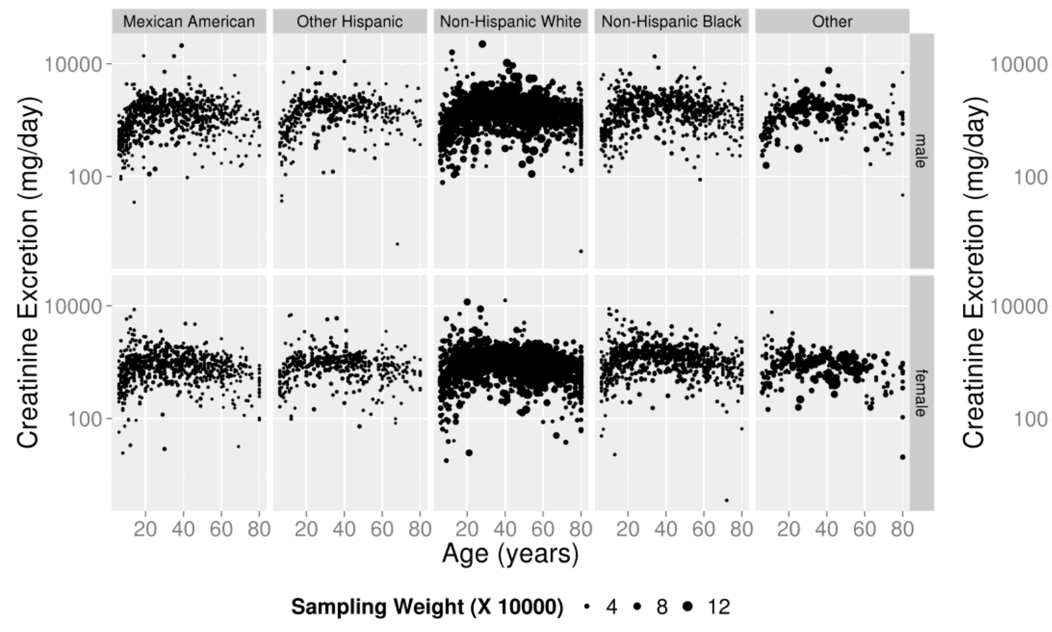
Model for $\log_{10}$ (CER)

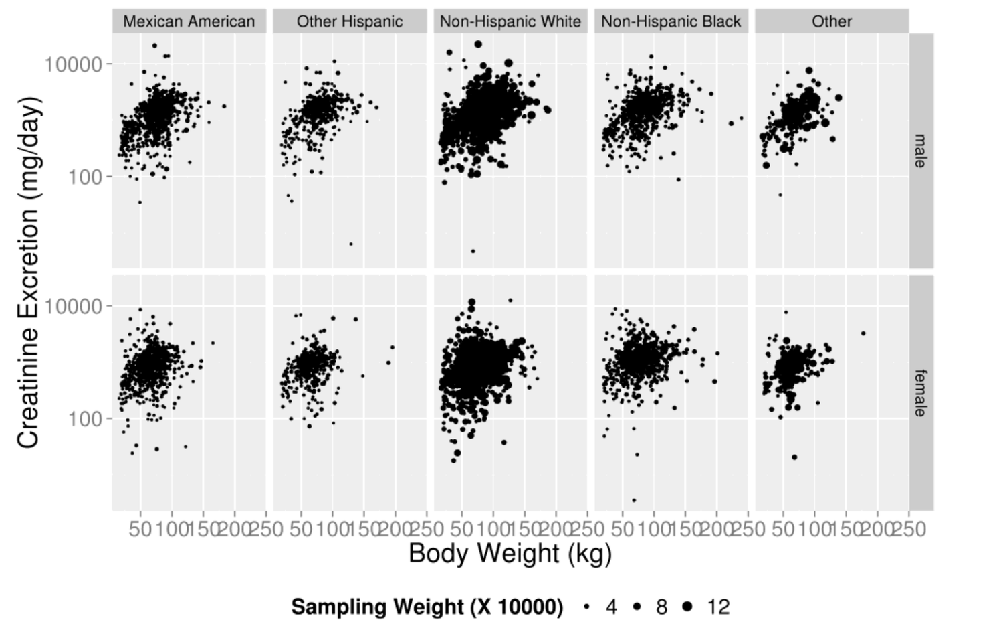
$$\log_{10}(\text{CER}) = M_{\text{Gender}} + D_{\text{Ethnicity}} + ns(\text{Age}, \text{knots}=c(20, 60)) + ns(\text{Bwt}, \text{knots} = c(50, 100)) + s \times E$$

$E \sim t(df = 3.5)$

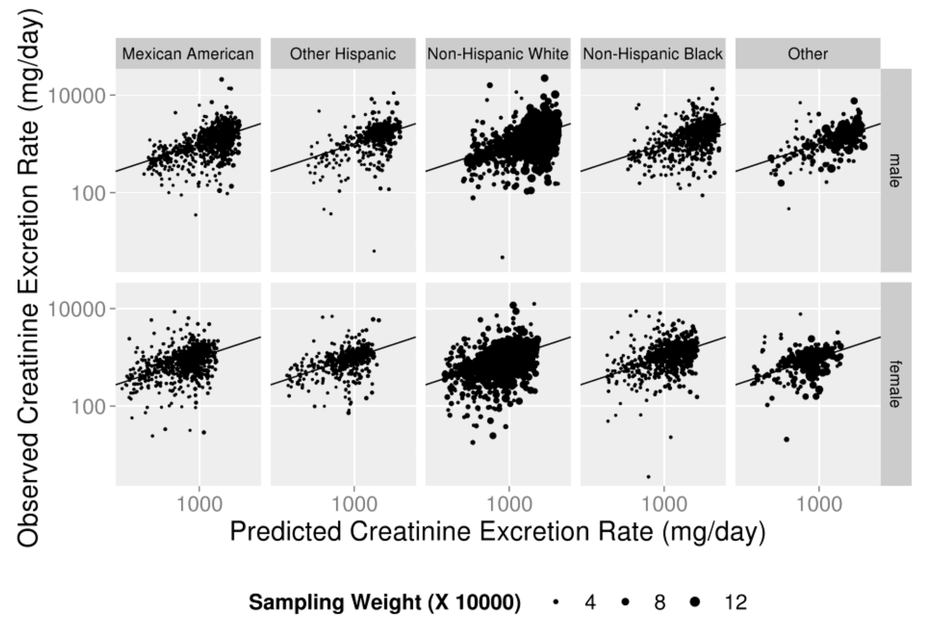
ns = natural cubic spline

t = Student's *t* distribution with *df* degrees of freedom (to handle "outliers")





Daily creatinine excretion inferred from NHANES urine volumes



Evaluating model fit

This QR code encodes the R function for calculating creatinine excretion rate.

Parameter Estimates

Parameter	Estimate (95% CI)	P-value (H0: parameter = 0)
$M_{\text{Female Mexican American}}$	2.48 (2.45, 2.51)	< 0.001
$M_{\text{Male Mexican American}}$	2.63 (2.59, 2.66)	< 0.001
$D_{\text{Other Hispanic}}$	0.039 (0.00879, 0.6850)	0.011
$D_{\text{Non-Hispanic White}}$	0.062 (0.0401, 0.0842)	< 0.001
$D_{\text{Non-Hispanic Black}}$	0.096 (0.0746, 0.1180)	< 0.001
D_{Other}	0.035 (0.0129, 0.0577)	0.002
Bwt_1	0.46 (0.414, 0.511)	< 0.001
Bwt_2	0.79 (0.637, 0.936)	< 0.001
Bwt_3	0.22 (0.0016, 0.432)	0.048
Age_1	0.011 (-0.0106, 0.0319)	0.32575
Age_2	0.089 (0.0363, 0.143)	< 0.001
Age_3	-0.24 (-0.270, -2.17)	< 0.001

ESTIMATING EXPOSURE FROM URINE SAMPLES

A Model for Estimating Population (Geometric) Mean Parent Chemical Exposure from Urinary Measurements of Metabolites

Assume exposures to parent chemicals are homogeneous over time for any given individual: as in a steady-state infusion dosing scheme. Then, urinary output is at steady state as well.

Urinary metabolites may originate from the metabolism of multiple parent compounds. For example,
Assuming 100% absorption, and that all exposure molecules are accounted for (important assumptions), concentration of urinary metabolite *j*, U_j is

$$U_j = \sum_{i=1}^{n} \phi_{ij} P_i$$

Here, ϕ_{ij} is the proportion of absorbed molecules of chemical that are excreted and detected as metabolite *j*. When all of a parent compound *i* is metabolized to a single metabolite *j*, or is excreted unmetabolized, then ϕ_{ij} = 1 for that particular parent-metabolite pair, and ϕ_{ik} = 0 for all other metabolites *k*. More generally, if all exposure molecules are accounted for, then

$$\sum_{j=1}^{m} \phi_{ij} = M_i$$

where M_i is the number of metabolite molecules parent *i* generates. For instance, if a parent molecule is split into two new molecules, both of which appear in urine, then *M* is 2.

The P_i are unknown. The coefficients ϕ_{ij} are unknown, except to the extent they are constrained by the M_i's, which are assumed known. The U_j are estimated from NHANES data.

Estimating Population Geometric Mean Metabolite Urine Metabolite Excretion Rates

A subsample of just under 2000 NHANES participants contributed urine samples for chemical evaluation. Urine samples were analyzed for a range of metabolites of exposures of concerns, as well as for creatinine concentration. Resulting measurements are reported as either below a sample-specific limit of quantification or as the ratio of concentration of metabolite to concentration of creatinine. In the analysis reported here, gender, age, weight, and ethnicity-specific creatinine excretion rates (see panel to the lower left) were used to convert measurements to a daily excretion rate of the measured metabolites.

Data were taken directly from the publicly available CDC datafiles (http://www.cdc.gov/nchs/nhanes.htm). Utilities in the survey package (Lumley, 2004, 2012) were used to get maximum pseudo-likelihood estimates of population geometric means and population coefficients of variation (CV), using censored likelihoods to account for below-limit-of-detection observations.

Bayesian Estimates of Exposure Rates

Bayesian methods were used to estimate the distribution of exposure rates that are consistent with the observed estimates of population geometric mean metabolite concentrations and their uncertainty and the unknown quantitative relationships between parent exposure and metabolite excretion. The Hamiltonian Monte Carlo sampler, stan (Stan development team, 2013), was used to draw samples for probability distributions characterizing the uncertainty of the exposure rates.

Summary, Caveats, and Future Work

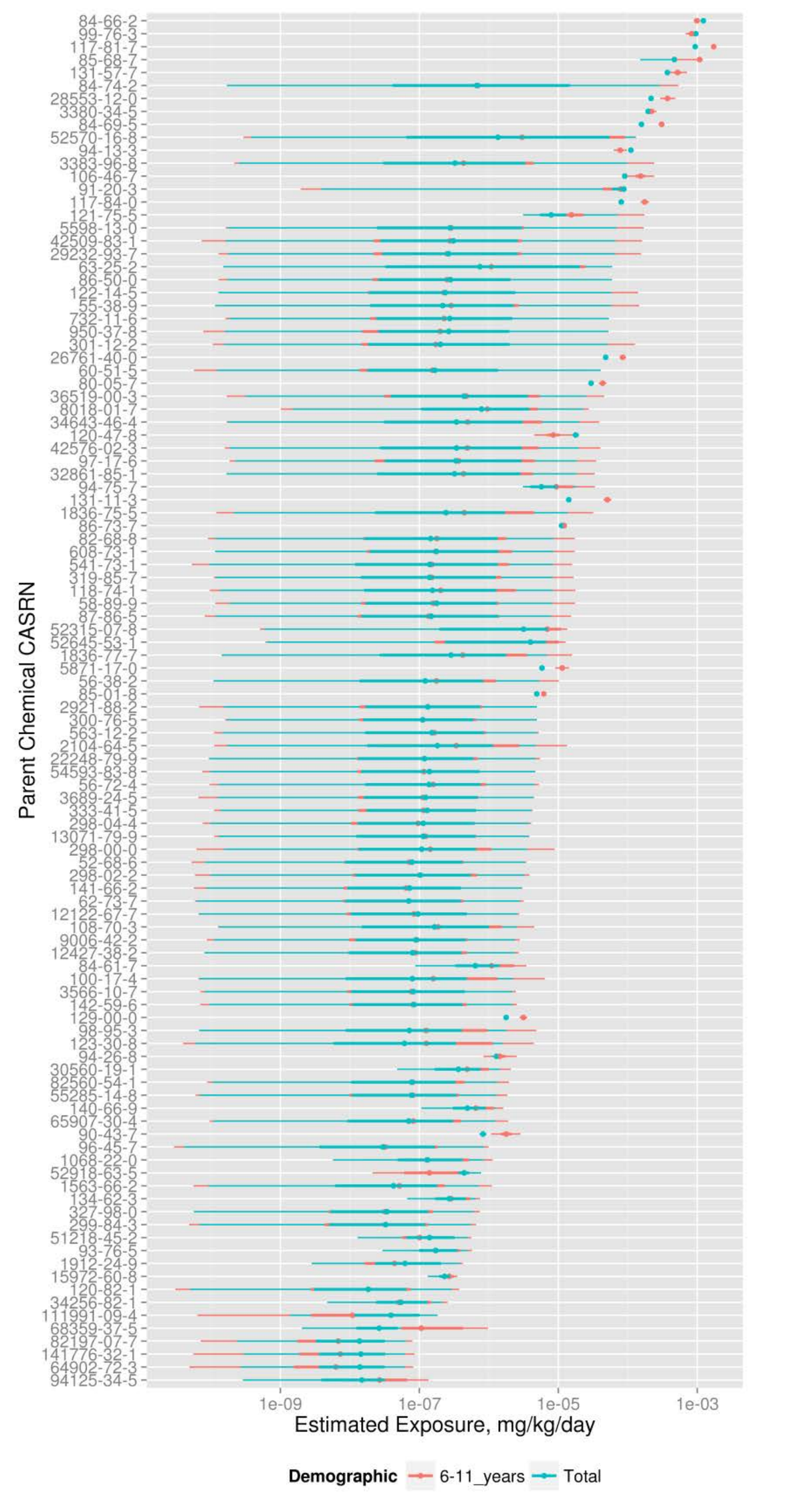
While estimates of exposure to individuals from samples collected at a single time point are problematic, it is possible to estimate population mean exposures from such sampling designs. The estimates in this poster depend on assumptions about the fraction of the exposed chemical recovered as metabolites in urine, and about the fraction of the exposure which is absorbed. Future work will attempt to characterize those fractions. The Bayesian framework used here adapts quite naturally to include statements of uncertainty about the fraction of parent recovered as metabolites (e.g., about 5% recovery, between about 1 % and 15%). The work described here assumes that exposure and elimination are at pseudo steady state. This may be reasonable for chemicals measured in urine, but may well not be for chemicals measured in serum (see Strope et al, poster 363, abstract # 2234m).

Metabolites Measured in NHANES Urine Samples

CASRN	Chemical Name	CASRN	Chemical Name	CASRN	Chemical Name
100-02-7	Paranitrophenol	30833-53-5	Mono-isobutyl phthalate (MiBP)	674808-38-9	Acetochlor mercapture
10265-92-6	Methamidophos	3380-34-5	Triclosan	7517-36-4	Mono-cyclohexyl phthalate (MCHP)
1068-22-0	Diethyldithiophosphate (DEDTP)	3739-38-6	3-phenoxybenzoic acid	756-80-9	Dimethyldithiophosphate (DMDTP)
1112-38-5	Dimethylthiophosphate (DMTP)	40321-98-0	Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)	7651-86-7	4-Hydroxyphenanthrene
111991-09-4	Nicosulfuron	40321-99-1	Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)	77279-89-1	Fluoro-phenoxybenzoic acid
116482-92-9	Alachlor mercapturate	40809-41-4	Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)	80-05-7	Bisphenol A
1190-28-9	Malathion diacid	4376-18-5	Mono-methyl phthalate (MMP)	813-78-5	Dimethylphosphate (DMP)
120-47-8	Ethyl paraben	4376-20-9	Mono-2-ethylhexyl phthalate (MEHP)	82197-07-7	Metsulfuron-methyl
120-83-2	2,4-Dichlorophenol	5315-79-7	1-Hydroxypyrene	87-86-5	Pentachlorophenol
131-57-7	Benzophenone-3	53179-78-5	cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylic acid	88-06-2	2,4,6-Trichlorophenol
131-70-4	Mono-n-butyl phthalate (MnBP)			90-15-3	1-Hydroxynaphthalene (1-Naphthol)
134-62-3	DEET	5393-19-1	Mono-n-octyl phthalate (MOP)	90-43-7	ortho-Phenylphenol
135-19-3	2-Hydroxynaphthalene (2-Naphthol)	55701-03-6	trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid	93-76-5	2,4,5-Trichlorophenoxyacetic acid
138722-96-0	Atrazine mercapturate			94125-34-5	Prosulfuron
140-66-9	4-tert-Octylphenol	55701-05-8	cis-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid	94-13-3	Propyl paraben
141776-32-1	Sulfosulfuron			94-26-8	Butyl paraben
1563-38-8	Carbofuranphenol	583-78-8	2,5-Dichlorophenol	94-75-7	2,4-Dichlorophenoxyacetic acid
159956-64-6	Metolachlor mercapturate	5871-17-0	Diethylthiophosphate (DETP)	95-95-4	2,4,5-Trichlorophenol
1689-64-1	9-Hydroxyfluorene	598-02-7	Diethylphosphate (DEP)	96-45-7	Ethylene thiourea
2306-33-4	Mono-ethyl phthalate (MEP)	605-55-0	2-Hydroxyphenanthrene	99-76-3	Methyl paraben
2433-56-9	1-Hydroxyphenanthrene	605-87-8	3-Hydroxyphenanthrene	MCNP	Mono-(carboxynonyl) phthalate (MCNP)
2443-58-5	2-Hydroxyfluorene	6344-67-8	3-Hydroxyfluorene	MCOP	Mono-(carboxyoctyl) phthalate (MCOP)
2528-16-7	Mono-benzyl phthalate (MBzP)	64902-72-3	Chlorsulfuron	MiNP	Mono-isononyl phthalate (MiNP)
30560-19-1	Acephate	66851-46-5	Mono-(3-carboxypropyl) phthalate (MCPP)		

Parental Compounds Associated with Metabolites Measured in NHANES Urine Samples

CASRN	Chemical Name	Associated Metabolite CAS	CASRN	Chemical Name	Associated Metabolite CAS
100-17-4	4-Nitroanisole	100-02-7	42576-02-3	Bifenox	120-83-2
106-46-7	para-Dichlorobenzene	583-78-8	51218-45-2	Metolachlor	159956-64-6
1068-22-0	Ammonium ethyl phosphorodithioate	1068-22-0	52315-07-8	Cypermethrin	3739-38-6, 55701-03-6, 55701-05-8
108-70-3	1,3,5-Trichlorobenzene	88-06-2	52570-16-8	Naproanilide	135-19-3
111991-09-4	Nicosulfuron	111991-09-4	52645-53-1	Permethrin	3739-38-6, 55701-03-6, 55701-05-8
117-81-7	Di-2-ethylhexyl phthalate	40321-98-0, 40321-99-1, 40809-41-4, 4376-20-9	52-68-6	Trichlorfon	813-78-5
117-84-0	Di-n-octyl phthalate	66851-46-5, 5393-19-1	52918-63-5	Deltamethrin	3739-38-6, 53179-78-5
118-74-1	Hexachlorobenzene	87-86-5, 88-06-2, 95-95-4	541-73-1	1,3-dichlorobenzene	120-83-2
120-47-8	Ethyl paraben	120-47-8	54593-83-8	Chlorethoxyphos	598-02-7
120-82-1	1,2,4-Trichlorobenzene	95-95-4	55285-14-8	Carbosulfan	1563-38-8
12122-67-7	Zineb	96-45-7	55-38-9	Fenthion	1112-38-5, 813-78-5
121-75-5	Malathion	1112-38-5, 1190-28-9, 756-80-9, 813-78-5	5598-13-0	Chlorpyrifos methyl	1112-38-5, 813-78-5
122-14-5	Fenitrothion	1112-38-5, 813-78-5	563-12-2	Ethion	598-02-7
123-30-8	4-Aminophenol	100-02-7	56-38-2	Parathion	100-02-7, 598-02-7
12427-38-2	Maneb	96-45-7	56-72-4	Coumaphos	598-02-7
129-00-0	Pyrene	5315-79-7	5871-17-0	Phosphorothioic acid	5871-17-0
13071-79-9	Terbufos	598-02-7	58-89-9	Lindane	87-86-5, 88-06-2, 95-95-4
131-11-3	Dimethyl phthalate	4376-18-5	60-51-5	Dimethoate	1112-38-5, 756-80-9, 813-78-5
131-57-7	Benzophenone-3	131-57-7	608-73-1	Hexachlorocyclohexane	87-86-5, 88-06-2, 95-95-4
134-62-3	N,N-Diethyl-3-methylbenzamide	134-62-3	62-73-7	Dichlorvos	813-78-5
140-66-9	4-tert-Octylphenol	140-66-9	63-25-2	Carbaryl	90-15-3
141-66-2	Dicrotophos	813-78-5	64902-72-3	Chlorsulfuron	64902-72-3
141776-32-1	Sulfosulfuron	141776-32-1	65907-30-4	Furathiocarb	1563-38-8
142-59-6	Nabam	96-45-7	68359-37-5	Cyfluthrin	55701-03-6, 55701-05-8, 77279-89-1
1563-66-2	Carbofuran	1563-38-8	732-11-6	Phosmet	1112-38-5, 756-80-9, 813-78-5
15972-60-8	Alachlor	116482-92-9	80-05-7	Bisphenol A	80-05-7
1836-75-5	Nitrofen	100-02-7, 120-83-2	8018-01-7	Mancozeb	96-45-7
1836-77-7	Chlornitrofen	100-02-7, 88-06-2	82197-07-7	Metsulfuron-methyl	82197-07-7
1912-24-9	Atrazine	138722-96-0	82560-54-1	Benfuracarb	1563-38-8
2104-64-5	EPN	100-02-7	82-68-8	Pentachloronitrobenzene	87-86-5, 88-06-2, 95-95-4
22248-79-9	Tetrachlorvinphos	813-78-5	84-61-7	Dicyclohexyl phthalate	7517-36-4
26761-40-0	Di-isodecyl phthalate	MCNP	84-66-2	Diethyl phthalate	2306-33-4
28553-12-0	Di-isononyl phthalate	MCOP, MiNP	84-69-5	Di-isobutyl phthalate	30833-53-5
2921-88-2	Chlorpyrifos	598-02-7	84-74-2	Dibutyl phthalate	131-70-4
29232-93-7	Pirimiphos-methyl	1112-38-5, 813-78-5	85-01-8	Phenanthrene	2433-56-9, 605-55-0, 605-87-8, 7651-86-7
298-00-0	Methyl parathion	100-02-7, 1112-38-5, 813-78-5	85-68-7	Benzylbutyl phthalate	131-70-4, 2528-16-7
298-02-2	Phorate	598-02-7	86-50-0	Azinphos methyl	1112-38-5, 756-80-9, 813-78-5
298-04-4	Disulfoton	598-02-7	86-73-7	Fluorene	1689-64-1, 2443-58-5, 6344-67-8
299-84-3	Fenchlorphos	95-95-4	87-86-5	Pentachlorophenol	87-86-5, 88-06-2, 95-95-4
300-76-5	Naled	813-78-5	9006-42-2	Metiram	96-45-7
301-12-2	Oxydemeton-methyl	1112-38-5, 813-78-5	90-43-7	ortho-Phenylphenol	90-43-7
30560-19-1	Acephate	10265-92-6, 30560-19-1	91-20-3	Naphthalene	135-19-3, 90-15-3
319-85-7	beta-Hexachlorocyclohexane	87-86-5, 88-06-2, 95-95-4	93-76-5	2,4,5-Trichlorophenoxyacetic acid	93-76-5
327-98-0	Trichloronate	95-95-4	94125-34-5	Prosulfuron	94125-34-5
32861-85-1	Chlomethoxyfen	120-83-2	94-13-3	n-propyl paraben	94-13-3
333-41-5	Diazinon	598-02-7	94-26-8	Butyl paraben	94-26-8
3380-34-5	Triclosan	3380-34-5	94-75-7	2,4-Dichlorophenoxyacetic acid	120-83-2, 94-75-7
3383-96-8	Temephos	1112-38-5, 813-78-5	950-37-8	Methidathion	1112-38-5, 756-80-9, 813-78-5
34256-82-1	Acetochlor	674808-38-9	96-45-7	Ethylene thiourea	96-45-7
34643-46-4	Prothiofos	120-83-2	97-17-6	Dichlofenthion	120-83-2
3566-10-7	Amobam	96-45-7	98-95-3	Nitrobenzene	100-02-7
36519-00-3	Phosdiphen	120-83-2	99-76-3	Methyl paraben	99-76-3
3689-24-5	Sulfotepp	598-02			
42509-83-1	Isazaphos-methyl	1112-38-5, 813-78-5			



Estimated dose rates of parental compounds associated with metabolites measured in NHANES urine samples, in the total population, and among 6-11 year-olds. Central points are medians, thick lines run from 25%-ile to 75%-ile, thin lines run from 2.5%-ile to 97.5 %-ile.

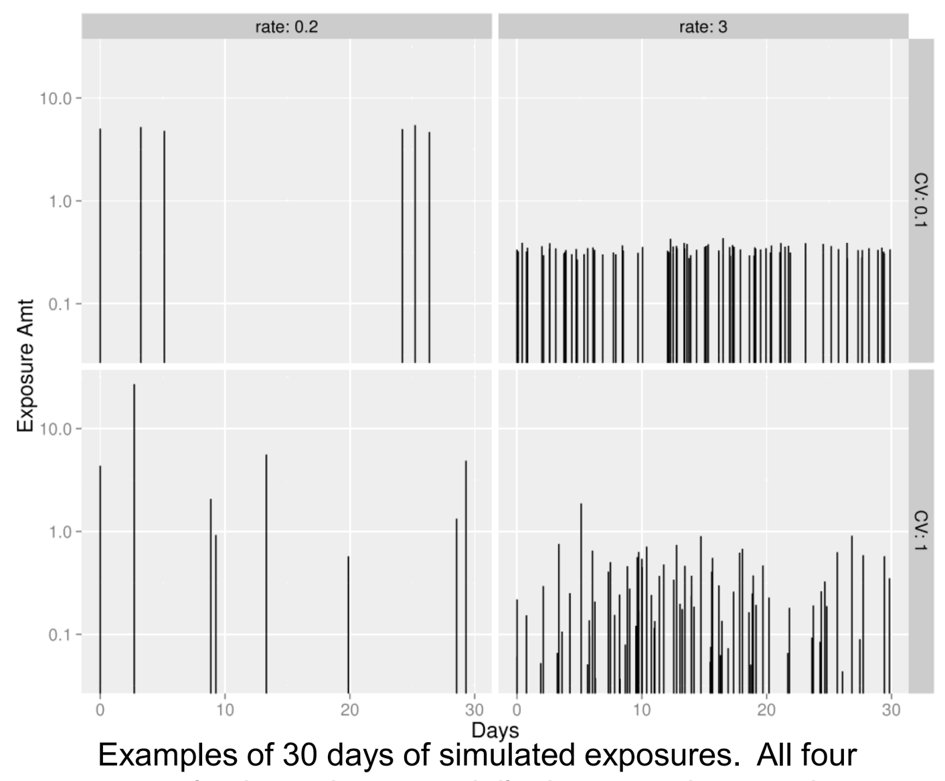
RELAXING THE STEADY STATE ASSUMPTION

The population exposure inferences were made assuming a constant steady-infusion dose. What if we relax that to a simpler, more plausible exposure model, still with constant long-term exposure rate, but with some variability in exposure from time to time, and no population variability in pharmacokinetics? This simulation addresses two questions:

- Does the geometric mean estimated under the stochastic exposure scenario match the real geometric mean dose?
- What does the variance among single urine samples look like, and how does that compare to that observed in the NHANES data?

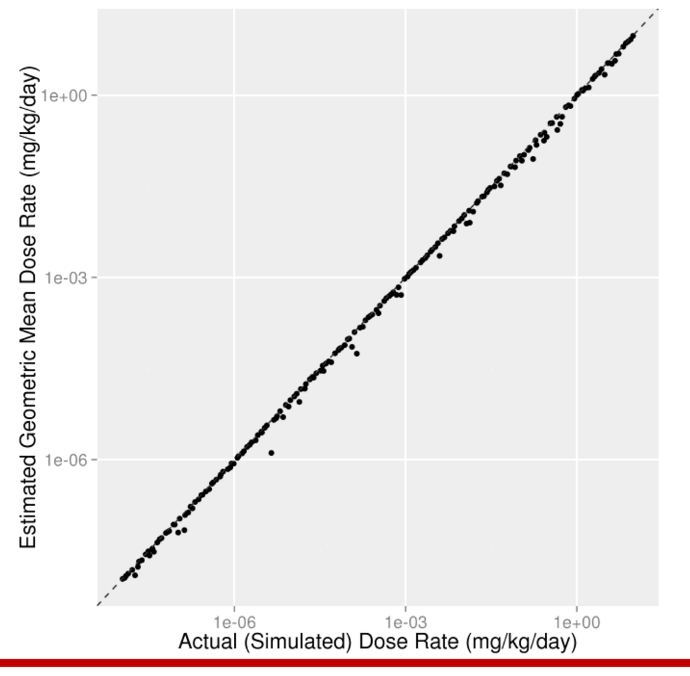
Approach to the Simulation

- Simulate exposure events as occurring at random (exponential waiting times), given by simulation parameter *rate*.
- The exposure amount is assumed to be lognormally distributed with specified CV (given by simulation parameter *CV*). For a given exposure event rate, the median of the exposure distribution is computed to give a fixed long-term average dose rate (given by the simulation parameter *dose*).
- The exposure amount is used as input into a one compartment model with absorption half-life *th.a* and elimination half-life *th.e*. Time between voids is random, uniformly distributed between 2 and 3 hours.
- For each set of parameter values, collect 1000 samples.
- Estimate geometric mean and CV using maximum likelihood
- Select 200 sets of parameter values in an Optimum Latin Hypercube design from the ranges:
  - th.e: 1 hr – 14 weeks
  - th.a: 1 – 12 hours
  - CV .1 – 4
  - dose: 10^{-8} – 10 mg/kg/day
  - rate: .1/day – 6/day



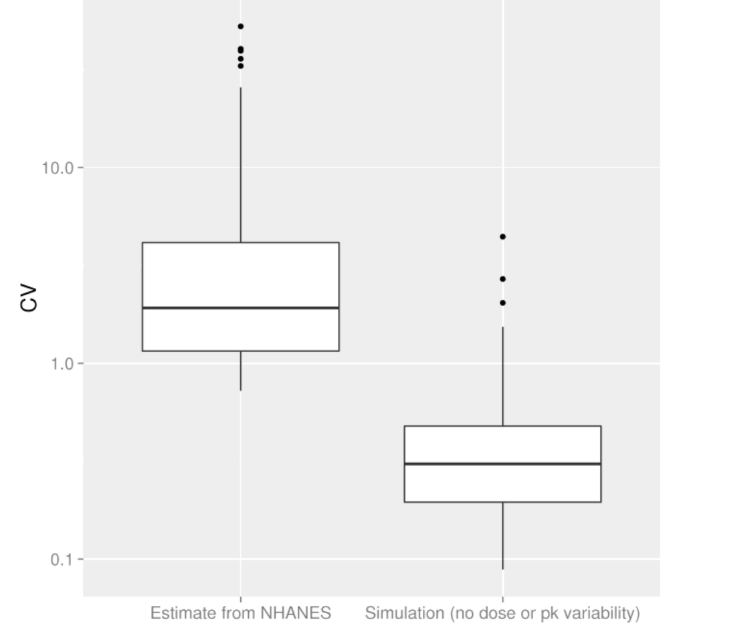
Examples of 30 days of simulated exposures. All four examples have the same daily dose rate, but vary in the daily rate of exposure events (*rate*) and CV for exposure amount).

As the frequency of exposure events increases, urine measurements look less variable, because the time-to-time variability is smoothed out.



ESTIMATES FROM NHANES URINE MEASUREMENTS CAN BE INTERPRETED AS ESTIMATES OF POPULATION GEOMETRIC MEAN EXPOSURES

Over 9 orders of magnitude of dose rate, the estimated population geometric mean of simulated urine measurements closely match the administered dose rate, over a plausibly wide range of elimination and absorption rates, exposure event rates and variability of the magnitude of exposure events. This is consistent with Ayleward et al (2012)



Little of the observed population variability in NHANES urinary measurements is likely to be due to the sorts of stochastic aspects considered in this simulation. This leaves real variability in exposure and pharmacokinetics as the important contributors to the variability measured in NHANES.

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