**Using a Physiologically Based Pharmacokinetic Model to Link Urinary Biomarker Concentrations to Dietary Exposure of Perchlorate**

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**Abstract**

To assess human exposures to perchlorate, several studies have attempted to estimate average daily intakes using two approaches: (1) directly by multiplying perchlorate concentrations in food by food consumption rates; or (2) indirectly from urinary perchlorate concentrations. These approaches provided population-based estimates, but the usefulness of urinary biomarker data for predicting exposures at the individual level has not been demonstrated for perchlorate. Thus, the objective of this study was to evaluate the consistency of urine biomarker concentrations with intake-based exposure estimates. Specifically, two analyses were conducted: (1) using data from a controlled human study to examine the ability of a physiologically based pharmacokinetic (PBPK) model to predict perchlorate concentrations in single-spot and cumulative urine samples; and (2) using biomarker data from a population-based study and a PBPK model to demonstrate the challenges in linking urinary biomarker concentrations to intake doses for individuals. Results showed that the modeling approach was able to characterize the distribution of biomarker concentrations at the population level, but predicting the exposure-biomarker relationship for individuals was much more difficult. The type of information needed to reduce the uncertainty in estimating intake doses, for individuals, based on biomarker measurements is discussed.

**Keywords**

Perchlorate; Biomarker; Physiologically Based Pharmacokinetic Modeling; Dietary Exposure

## *1. Introduction*

Perchlorate is used primarily as an oxidizer in solid rocket fuels and propellants (Mendiratta et al. 1996). It is also used in explosives, pyrotechnics, and blasting formulations (NAS 2005). Besides industrial uses, perchlorate has been used to diagnose thyroid disease and to treat hyperthyroidism associated with Graves' disease (EPA 2002). The environmental occurrence of perchlorate can also originate from natural sources; for example, it can be formed in the atmosphere and during the drinking water disinfection process (Orris et al. 2003; Dasgupta et al. 2005; Rajagopalan et al. 2006; Rao et al. 2007; Rajagopalan et al. 2009; Rao et al. 2010).

Perchlorate can potentially affect thyroid function by inhibiting iodide transport into thyroid follicular cells, resulting in a decrease of iodide available for synthesis of thyroid hormones. Thyroid hormones are critical in regulating metabolic activities in adults, as well as growth and development in fetuses and infants. Severe hypothyroidism during pregnancy can cause permanent cognitive impairment of the fetus (Crooks et al. 1960; Glinoer 2000), while mild hypothyroidism has been associated with subtle cognitive deficits in children (Klein et al. 2001; Haddow et al. 2002). Several recent epidemiological studies have associated perchlorate exposure with statistically significant changes in thyroid hormone levels (Blount et al. 2006; Cao et al. 2010; Steinmaus et al. 2010), but there is no consistent evidence for adverse outcomes in healthy adults , healthy infants/newborns (Blount et al. 2009), or even pregnant women with low iodine intake (Gibbs et al. 2008; Pearce et al. 2011). Nonetheless, due to the potential for neurological development impairment *in utero*, women of child-bearing age have been identified as a potentially susceptible population.

Perchlorate has a low vapor pressure and can be rapidly absorbed from the gastrointestinal tract, so the primary route of concern is ingestion through food and drinking water (EPA 2002). To assess health risks from perchlorate exposures, many studies have estimated an average daily intake dose for

comparison with the U.S. Environmental Protection Agency's (EPA) Reference Dose (RfD) (0.7 µg/kg-day). Daily intake of perchlorate have been estimated using two approaches: (1) directly by multiplying perchlorate concentrations in food by food consumption rates (EPA 2002; Blount et al. 2007; Murray et al. 2008; Sanchez et al. 2009; Mendez et al. 2010); or (2) indirectly from urinary perchlorate concentrations (Blount et al. 2007; Lorber 2009; Blount et al. 2010; Mendez et al. 2010; English et al. 2011; Valentin-Blasini et al. 2011).

Murray and colleagues estimated average daily intakes of perchlorate for the U.S. population (0.08 to 0.39 µg/kg-day) based on the perchlorate concentrations in food from the U.S. Food and Drug Administration's (FDA) Total Diet Study (TDS)[1] and average per capita food consumption (Murray et al. 2008). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) estimated an average intake dose of 0.1 µg/kg-day from both food and drinking water (JECFA 2010). Sanchez and colleagues estimated an average intake dose of 0.096 µg/kg-day for individuals living in the lower Colorado River region (LCRR)[2] by matching the consumption data in DEEM™[,3] to residue concentrations from crops sampled in the LCRR (Sanchez et al. 2009). Blount and colleagues estimated a median intake of 0.0091 µg/kg-day from tap water for participants in the Centers for Disease Control and Prevention's (CDC) National Health and Nutrition Examination Survey (NHANES) in 2005-2006 based on measured perchlorate concentrations in tap water, self-reported tap water consumption data, and measured body weight (Blount et al. 2010). The result suggested that, in general, tap water is a minor contributor to

[1] Total Diet Study (TDS) provides baseline information on the levels of nutrients and contaminants in the U.S. food supply.

[2] Population in the LCRR may have higher exposure to perchlorate due to ammonium perchlorate manufacturing activities in Nevada.

[3] DEEM™ (Dietary Exposure Evaluation Model) is a dietary exposure analysis system that may be used to estimate exposure to constituents in foods comprising the diets of the U.S. population. Food consumption data in this model comes from the Continuing Survey of Food Intakes by Individuals (CSFII) conducted in 1989-1992 and in 1994-1996.

total perchlorate exposure (Blount et al. 2010). Mendez and colleagues estimated, for women of child-bearing age, median intake doses of 0.055 and 0.057-0.068 µg/kg-day for food-only and food/water exposures, respectively, using the LifeLine™, [4] exposure model (Mendez et al. 2010).

Perchlorate intake doses have also been estimated indirectly from urinary perchlorate concentrations, such as those measured in NHANES 2001-2002 (Blount et al. 2007; Lorber 2009; Huber et al. 2010; Mendez et al. 2010). In NHANES 2001-2002, perchlorate was detected (detection limit = 0.05 µg/L) in all 2820 single-spot urine samples (median = 3.6 µg/L). For women of child-bearing age (n = 662), the median was 2.9 µg/L. Using a creatinine correction approach (Mage et al. 2004), Blount and colleagues estimated a median intake dose of 0.066 µg/kg-day for all adults based on urinary perchlorate concentrations, urinary creatinine concentrations, and an estimated daily creatinine excretion rate (Blount et al. 2007). Using a different daily creatinine excretion rate (Mage et al. 2008), Mendez and colleagues estimated a median intake dose of 0.056 µg/kg-day for women of child-bearing age (Mendez et al. 2010). Huber and colleagues estimated median intake doses of 0.08, 0.053, 0.061 µg/kg-day for those residing in counties where the drinking water system had detectable perchlorate, were not sampled, and had no detectable perchlorate, respectively (Huber et al. 2010). Instead of the creatinine correction approach, Lorber developed a two-compartment pharmacokinetic model to back-calculate a daily intake dose of 0.064 µg/kg-day based on the median urinary concentration of 3.6 µg/L (Lorber 2009).

Urinary perchlorate concentrations have also been used to estimate intake doses for highly-exposed or sensitive populations. English and colleagues estimated intake doses (0.02 to 0.5 µg/kg-day) for 31 individuals residing in the LCRR (urinary concentrations: 1.1 to 32.2 µg/L) (English et al. 2011). Valentin-

[4] LifeLine™ is a software that predicts population-based aggregate and cumulative exposures from chemical residues in food, tapwater, and residual settings (Price et al. 2005)

Blasini and colleagues estimated an intake dose of 0.2 μg/kg-day for 92 infants (median urinary concentration: 0.6 – 3.9 μg/L) (Valentin-Blasini et al. 2011). These biomonitoring studies estimated a population distribution of daily intakes of perchlorate based on a population distribution of biomarker data. The comparability of the intake estimates from the direct (intake-based) and indirect (excretion-based) approaches suggests that both can be useful at the population level. However, the usefulness of urinary biomarker data for predicting intakes at the individual level has not been demonstrated for a compound with a short half-life, like perchlorate. Thus, the objective of the current study was to evaluate the consistency of urinary biomarker concentrations with intake-based intake estimates using best available information on exposures and pharmacokinetics. For perchlorate, available information includes individual biomarker measurements, individual food consumption patterns, estimated residues in food from a population study, and a physiologically based pharmacokinetic (PBPK) model that describes the time course of absorption, distribution, metabolism and excretion of perchlorate. Specifically, two analyses were conducted: (1) Using data from a controlled human study (Greer et al. 2002), the ability of the PBPK model to predict perchlorate concentrations in single-spot and cumulative urine samples was estimated; and (2) Using a sub-set of biomarker data from NHANES 2001-2002 and the PBPK model, the challenges in linking urinary biomarker concentrations to intake doses for individuals were determined.

## *2. Methods*

### 2.1 Measurement of perchlorate in urine – Controlled Human Study (Greer study)

A human dose-response study for perchlorate inhibition of thyroidal iodide uptake (Greer et al. 2002) was selected to evaluate the ability of the PBPK model to predict biomarker concentrations in single-spot and cumulative urine samples. In the Greer study, male and female volunteers (18 to 57 years old)

were given perchlorate in 400 mL drinking water at doses of 0.007, 0.02, 0.1, or 0.5 mg/kg-day for 14 consecutive days. Each volunteer was instructed to drink 100 mL at 0800, 1200, 1600, and 2000 hr on each perchlorate ingestion day. Volunteers were also asked to report the time and volume of each ingestion for additional verification, but these compliance data were not available to us. The lowest dose of 0.007 mg/kg-day is at least three orders of magnitude higher than the average perchlorate intakes estimated from food and water (Murray et al. 2008; Blount et al. 2010), so dietary and drinking water exposure was inconsequential. Whole blood, serum, and urine samples were collected from each volunteer to be analyzed for eight- and 24-h accumulated thyroidal radioiodine, thyroid function, serum chemistry and hematology (Greer et al. 2002). In addition, 24-h urine samples were collected on the following days: before exposure, on exposure days 1, 2, 8, 14, and up to three days after exposure (*i.e.*, days 15, 16, and 17). In a later study (Merrill et al. 2005), urine samples from dose groups 0.02 (n = 5), 0.1 (n = 7), and 0.5 (n = 8) mg/kg-day were analyzed for perchlorate concentrations. Thus, these were the only available biomarker data for our analyses. In addition, information on time/volume of urine voids was also available.

**2.2 Measurement of perchlorate in urine – General population survey (NHANES)**

NHANES 2001-2002 was selected to examine if a PBPK model can be used to predict individual urinary perchlorate concentrations based on individual dietary information collected in NHANES and estimated perchlorate concentrations in foods from the TDS. In NHANES 2001-2002, spot urine samples collected from 2820 individuals were analyzed for perchlorate, creatinine, and other chemicals (Blount et al. 2007). Study participants also provided information regarding their sociodemographic status, medical histories, and a food frequency questionnaire detailing their 24-h dietary recall. The dietary recall includes the time, amount, and type of food consumed during the 24 h period from midnight to midnight. No dietary

information was recorded between midnight and the time of urine collection, except for how long participants had fasted before urine collection. Some study participants were asked to fast for this time period, depending on which additional specimens were collected at the mobile exam center. Other information collected in NHANES included total tap water consumed the day before; source of tap water; water treatment devices used; dietary supplement usage; typical milk consumption; and when the spot urine sample was collected. Although the exact sample collection time was recorded, CDC only publicly releases, due to privacy concerns, the time information in sessions: morning (8:00 am – 12:30 pm), afternoon (1:30 pm – 5:30 pm), or early evening (5:30 pm – 9:30 pm).

Among those 2820 study participants, 1485 were females, 662 of which were at child-bearing age (15 – 44 years old) during the study period (Blount et al. 2007). The current study focused only on the susceptible population – women of child-bearing age.

*2.2.1 Estimation of dietary intake of perchlorate for the NHANES participants*

To reduce the uncertainties that arise from the missing dietary information between midnight and the time of urine collection, our study included only non-pregnant, non-lactating women of child-bearing age who reported fasting between the end of the dietary questionnaire time period and when single-spot urine samples were taken (n = 340). Dietary perchlorate intake for each of the 340 women was estimated by mapping the individual 24-h dietary recall entries to perchlorate residues measured in the TDS. The current TDS food list was compiled in 2003 based on the U.S. Department of Agriculture's 1994-1996, 1998 CSFII (94-98 CSFII) (Egan et al. 2007). During the 94-98 CSFII, survey participants reported detailed food consumption information on about 6,000 different foods, including beverages. To select representative TDS foods, the survey foods were first grouped by the similarity of their primary ingredients, and then the food consumed in greatest quantity from each group was selected to be the

representative. In all, 285 foods and beverages are included in the current TDS food list to represent all major components of an average American diet. After the TDS foods were selected, a mapping file was created to link each survey food code to the appropriate TDS food. Since the food coding scheme used in the CSFII is similar to that used in NHANES, this mapping file was updated to include new foods reported in NHANES to link the TDS residues concentrations to all foods reported in the NHANES dietary records.

Perchlorate concentrations in foods and beverages used to estimate dietary exposure in our study were based on analytical results of the TDS samples collected between 2005 and 2006. For a food item that had detectable perchlorate in all samples, one average concentration was calculated. For a food item that had one or more non-detects, three separate average concentrations were calculated by assuming these non-detect samples had a concentration of zero, half of the limit of detection (LOD), or LOD. For example, all raw banana samples were below the detection limit, so the three average concentrations calculated for raw banana were: zero (average of zero), 0.5 µg/kg (average of the half of LOD), and 1 µg/kg (average of LOD, which is 1 µg/kg). Perchlorate concentration in a specific food was then multiplied by the gram weight of food recorded in the 24-h dietary recall to calculate the amount of perchlorate consumed by the NHANES participants.

### 2.3 Physiologically based pharmacokinetic (PBPK) model for perchlorate

The PBPK model adapted for this study describes perchlorate and iodide kinetics across various life stages in humans (*e.g.*, pregnant women, children) (Clewell et al. 2007). This model was constructed based on a suite of PBPK models that were previously published for adult male, pregnant, lactating, fetal, and neonatal rats, as well as adult humans (Clewell et al. 2003a; Clewell et al. 2003b; Merrill et al. 2003; Merrill et al. 2005). The model included compartments for thyroid, skin, gastrointestinal (GI) tract, liver,

kidneys, fat, blood, mammary gland, placenta, milk, rapidly and slowly perfused tissues for adults (Figure 1), and sub-PBPK models for fetus and neonates. First order kinetics was used to describe both oral uptake (via drinking water and diet) and urinary clearance. The distribution of perchlorate to tissue compartments was described using either diffusion-limited (e.g., skin) or flow-limited (e.g., kidneys and fat) kinetics. Active uptake of perchlorate was included for thyroid, mammary gland, and GI compartments. The model assumes no metabolism of perchlorate and 100% excretion of the ingested perchlorate in urine. Since the current study only examines urinary perchlorate concentrations for women of child-bearing age, the fetal and neonatal sub-models were not used. Detailed descriptions of the perchlorate PBPK models can be found elsewhere (Clewell et al. 2003a; Clewell et al. 2003b; Merrill et al. 2003; Merrill et al. 2005; Clewell et al. 2007). This model was programmed in ACSL 11.8 (The AEgis Technologies Group, Inc., Huntsville, AL).

### 2.4 Analyses of urinary biomarkers for perchlorate using the PBPK model

In the current study, two sets of PBPK model simulations were conducted to investigate the type of data/information needed to link urinary perchlorate concentrations with intake doses for individuals.

*2.4.1 Analyses of data from the controlled human study (Greer study)*

In the first analysis, the life-stage PBPK model (Clewell et al. 2007) was used to simulate perchlorate exposures with known doses in the Greer study (Greer et al. 2002). Since the actual time and volume of each ingestion were not available, the following scenario, which is based on instructions to volunteers, was used as model inputs: 100 % absorption from one quarter of a given dose (0.02, 0.1, or 0.5 mg/kg) at 0800, 1200, 1600, and 2000 hr for 14 consecutive days. The model predicted the time course of the amount of perchlorate excreted in urine over 15 days (14 days exposures + 1 day post-exposure). From

this time-course simulation, a cumulative amount of perchlorate in urine can be readily obtained for any given time interval. For each dose group, the model predicted (1) a 24-h cumulative amount of perchlorate; (2) a 48-h cumulative amount of perchlorate; and (3) a spot urine concentration. These three predictions were then compared with the observed data.

(1) The predicted 24-h cumulative amount of perchlorate in urine on exposure day 8 was compared with the 24-h cumulative amount measured on exposure day 8. The measured cumulative amount was calculated as the sum of the products of urine volume and urinary concentrations during the 24-h period.

(2) The predicted 48-h cumulative amount of perchlorate in urine on exposure days 8 and 14 were added together as a surrogate for a continuous 48-h cumulative amount of perchlorate in urine. This prediction was compared with the aggregated 24-h cumulative amount measured on exposure days 8 and 14.

(3) In the Greer study, the time-course of urinary perchlorate concentrations were available for each individual. In most cases, the individual's time and volume of each urine void were recorded. In some cases, the accumulative volumes of urine samples were reported over a known time period, as long as 4 hours. Based on these time-concentration profiles, the PBPK model was used to simulate the second void (as a spot urine concentration) on day 15 by dividing the simulated amount of perchlorate accumulated between the first and the second voids by the reported urine volume of the second void. This predicted spot urine concentration was compared with the measured urine concentration of the second void on day 15.

Note that the model inputs, for each individual, were the same every day, and thus, it predicted the same 24-h cumulative amount of perchlorate each exposure day. The selection of exposure days 8 and 14 was arbitrary; the comparison between model predictions and measurements can be conducted on any exposure day. It is the same with the selection of the second void on day 15 for the spot urine

comparison. Since the time and volume of each urine void were known in the Greer study, the comparison can be conducted with any spot urine sample.

*2.4.2 Analyses of data from the general population survey*

In the second analysis, the life-stage PBPK model (Clewell et al. 2007) was used to simulate dietary exposure of the 340 women from NHANES 2001-2002 (Blount et al. 2007). The current study did not include tap water consumption as a source of perchlorate exposure since several published studies suggested that drinking water is not a major contributor to total perchlorate intake (Blount et al. 2009; Huber et al. 2010; Mendez et al. 2010; EPA 2011). Urinary perchlorate concentrations for each individual were predicted using their dietary exposure profile constructed by mapping the dietary recall data to perchlorate concentrations in foods estimated from the TDS (Figure 2). While the TDS obtained market basket samples from different geographic regions in the U.S. in an attempt to be reasonably representative of national exposures, it is certainly possible that residue concentrations in foods consumed by the NHANES subjects were very different from average values derived in the TDS. Thus, using the TDS results as surrogates for individual intakes introduced several sources of uncertainty. One method to characterize uncertainty is Monte Carlo simulation, which involves running the model for a set of input/parameter combinations and estimating uncertainty from the model outputs at those combinations. To demonstrate such a method, the uncertainty associated with non-detect data in the TDS was evaluated as described below.

As described in Section 2.2.1, three average concentrations were calculated for TDS foods that had non-detect samples by assuming non-detects to be zero, half the LOD, or LOD. For each of these foods, a triangular distribution was generated based on the three average concentrations. When one of these foods was in a subject's food frequency questionnaire, a perchlorate concentration was randomly sampled from its triangular distribution. For each woman, this sampling process was repeated 100

times using Monte Carlo to obtain 100 sets of estimated perchlorate concentration for these foods at each meal. Based on the 24-h dietary recall, 100 intermittent perchlorate intake-time profiles were then constructed for each woman. The distribution of the 100 predicted urinary concentrations thus provides a quantitative measure of uncertainty associated with non-detects in the TDS.

The PBPK model simulated a seven-day perchlorate exposure for each individual to achieve pseudo steady-state. The 24-h intake-time profile was repeated for six days to simulate a continuous dietary exposure before the spot urine concentration was predicted on the 7th day (Figure 3). Dietary exposure ended on the 6th day at the last meal recorded in the 24-h dietary recall. Then, the PBPK model continued to run, without additional exposure, until the end of the self-reported fasting duration. The model-predicted rate of perchlorate excretion in urine (in μg/h) at this time point was divided by the rate of creatinine production (in g/h) to obtain a creatinine-normalized urine concentration (μg/g creatinine). The rate of creatinine production was calculated based on individual's age, height, and weight (data extracted from NHANES 2001-2002) using a modified Cockcroft-Gault equation (Mage et al. 2004). Model predictions were compared with the observed creatinine-normalized urine concentrations for individuals (*i.e.*, pair-wise comparison). In addition, a population-level comparison was made by treating the predicted and measured concentrations as two independent populations.

Pair-wise correlation analyses were conducted to determine whether the values of two variables were associated. Variables included in the analyses were total dietary intake of perchlorate (estimated from perchlorate concentrations in foods [TDS results] and the NHANES 24-h dietary recall), measured perchlorate concentrations in urine (μg/L), measured creatinine-normalized perchlorate concentrations in urine (μg/g creatinine), and model-predicted creatinine-normalized perchlorate concentrations in urine (μg/g creatinine). Two additional correlation analyses were conducted to demonstrate the impact

of uncertainties in the market basket measurements and human activities on our ability to link biomarkers to dietary exposures:

Subgroup 1 (uncertainty in market basket measurements): Seventy-nine women who reported to be a "milk drinker" and had consumed milk in their 24-h dietary recall. Milk drinkers were separated out for the following reasons: (1) estimated percent contribution from dairy products to total daily perchlorate intakes was about 20% for women of child-bearing age (Murray et al. 2008); and (2) perchlorate concentrations in milk were fairly consistent across the nation (Kirk et al. 2005; Murray et al. 2008; Sanchez et al. 2008), so that the actual milk concentrations consumed by the NHANES subjects may not be too different from the TDS estimates. Therefore, it was expected that the correlation between the predicted and measured perchlorate concentrations in urine would be stronger in milk drinkers.

Subgroup 2 (uncertainty in human activities): Two hundred and twelve women from whom urine samples were collected in the morning session (8:00 am – 12:00 pm). In NHANES 2001-2002, no dietary information was recorded from midnight to the time of urine sample collection. Although these 340 women reported fasting during this time period, inconsistencies were found when examining the time of last meal eaten, reported fasting duration, and urine sample collection session. For example, an individual who indicated the last meal was eaten at 10:00 pm (recorded in dietary recall) and whose urine sample was taken in the afternoon session (after 12:00 pm the next day) should have reported a fasting duration of at least 14 h. If this individual reported a fasting duration of 8 h, then when and what she ate would not be fully accounted for in the intake-time profile. Thus, 212 women who had their urine samples taken in the morning session were separated out because it is more likely that they did not eat before the urine sample collection. It was expected that the correlation between predicted and measured perchlorate concentrations in urine would be stronger in these 212 women than in all 340 women.

## *3. Results*

### 3.1 Analyses of data from the controlled human study

For each of the three doses, correlation coefficients between the predicted and measured perchlorate in urine were calculated for (1) a 24-h cumulative amount, (2) a 48-h cumulative amount, and (3) a spot urine concentration (Figure 4). In the high (0.5 mg/kg-day) and medium (0.1 mg/kg-day) dose groups, strong correlations (correlation coefficients larger than 0.75) were found for both cumulative amounts and spot urine concentrations. In the low dose group (0.02 mg/kg-day), the 48-h cumulative amount had a strong correlation (correlation coefficient: 0.8); the 24-h cumulative amount had a moderate correlation (correlation coefficient: 0.48); and the spot urine concentration had essentially no correlation (correlation coefficient: 0.12).

### 3.2 Analyses of data from the general population survey

In the current study, the dietary intakes of perchlorate for 340 women were estimated based on their 24-h dietary recall and estimated perchlorate residues in foods from the TDS. The average of the daily dietary intakes for these women was 0.1 μg/kg-day. The estimated 50th percentile was 0.075 μg/kg-day and the 95th percentile was 0.246 μg/kg-day. These estimates were similar to those previously estimated for the general population using food residue data and food consumption rates (Murray et al. 2008; JECFA 2010). When considering only the uncertainty in non-detects in the TDS samples, our Monte Carlo simulations showed that no more than two-fold difference was observed in the spread of the 100 simulated creatinine-adjusted urinary perchlorate concentrations. The coefficient of variation (standard deviation divided by mean) ranged from 3E-16 to 0.27.

The pair-wise comparison between predicted and measured creatinine-adjusted urinary perchlorate concentrations (μg/g creatinine) for each of the 340 women in NHANES 2001-2002 showed that the predictions did not agree well with measurements (Figure 5).

On the other hand, the population-level comparison between predictions and measurements was in good agreement. The distribution of the predicted creatinine-adjusted urinary concentrations was slightly lower than the distribution of the measured concentrations (Table 2). The distribution of the predictions had a mean of 2.78 and a 50th percentile of 2.03; while the distribution of the measurements had a mean of 3.42 and a 50th percentile of 2.58.

The results of our pair-wise correlation analyses are presented in Table 3. Good correlations (correlation coefficient: 0.66 to 0.69) were found between the measured urinary perchlorate concentrations with and without creatinine normalization, showing the effects of changing urine output and creatinine excretion. Weak correlations were found between total (24-h) dietary perchlorate intake (estimated from the TDS results and NHANES dietary recall) and measured creatinine-normalized perchlorate concentrations in urine (correlation coefficients: 0.16 to 0.34). Using these estimated dietary intakes as time-dependent inputs to the PBPK model, weak correlations (correlation coefficients: 0.19 to 0.30) were found between measured and predicted creatinine-normalized perchlorate concentrations.

The correlation between the predicted and measured urinary concentrations did not improve by separating out milk drinkers (correlation coefficients: 0.20 vs. 0.19; Table 3). The correlation between predicted and measured urinary concentrations was stronger in women whose samples were taken in the morning session (correlation coefficients: 0.23 vs. 0.20; Table 3), but the increase was not statistically significant.

## *4. Discussion*

The current study mapped the TDS analytical results and the NHANES dietary recalls to estimate the dietary intake for 340 women in NHANES 2001-2002. Our estimated average daily intake dose (0.1 μg/kg-day) was identical to those estimated using other food consumption rate assumptions (Murray et al. 2008; JECFA 2010). In addition, using these dietary intake-time profiles as model inputs, our predicted urinary perchlorate concentrations were comparable to biomarker measurements on a population basis (Table 2). The ability to characterize the central tendency and the distribution of biomarker concentrations suggested that our approach captured the aggregate variability and uncertainty in exposure patterns/pathways (*e.g.*, residues in food, amount of food consumed), pharmacokinetics (*e.g.*, body weight, tissue volume), and biomarker sample collection (*e.g.*, time of sample collection, urine outputs). In contrast, predicting the exposure-biomarker relationship for individuals was much more difficult.

For individual biomarker analysis, NHANES provided individual urinary perchlorate measurements and matching dietary recalls. The TDS provided estimates of perchlorate residues in food, using average concentrations from national surveys. The lack of correlation for predicted and measured individual biomarker results did not invalidate perchlorate biomarker measurements, dietary-based intake estimates, or the PBPK model predictions. Rather, the results showed that imprecision exists in each of these measurements and estimates, especially when key information is missing:

(1) Reporting errors in dietary recalls;

(2) No dietary information between midnight and the time of biomarker sampling;

(3) No information regarding urine volume and time of voids; and

(4) No direct measurements of perchlorate residues in food consumed by individuals.

While the current study did not an analysis of all sources of uncertainty, several steps were taken to reduce or evaluate some uncertainties (summarized below):

(1) Only women who reported fasting were included in this study to reduce the impact of unaccounted food consumption between midnight and biomarker sampling. In addition, women whose urine samples were collected in the morning session were separated out to represent a subgroup that were more likely to have actually fasted compared to those whose samples were taken after 12:30 pm. Our biomarker predictions for this subgroup, however, were not better than predictions for all women who reported fasting.

(2) The appropriate way to simulate urinary perchlorate concentration would be to integrate the PBPK model-predicted rate of perchlorate amount in urine (μg/h) between two voids, and then divide this cumulative amount by the urine volume of the last void. However, since both time and volume of urine voids were not available, the urinary concentration (in μg/g creatinine) was simulated by dividing the rate of amount (in μg/h) at a randomly selected time point by an estimated rate of creatinine production (in g/h).

(3) For uncertainties associated with food residues, two sources were examined: concentrations for non-detects and consistency of residue concentrations. For the non-detects, our Monte Carlo simulation showed that no more than a two-fold difference was observed in the spread of 100 simulated urinary concentrations. For the consistency of residue concentration, milk drinkers were separated out to represent a subgroup whose actual perchlorate intakes may be similar to the TDS averages. It was found, however, that the model predicted biomarker concentrations for this subgroup were not better than predictions for the entire group of women.

Besides these sources of uncertainty, it is possible that the use of a single spot urine sample also introduced uncertainty into the analysis of individual data. For NHANES, spot urine sample results from

multiple persons were averaged to provide population estimates such as geometric means and percentiles (Blount et al. 2007). For individual-level exposure estimates, however, other biomarker collection methods may be more appropriate. To investigate this hypothesis, the Greer study was used to evaluate the use of spot urine and cumulative urine samples for estimating intake doses. The Greer study was a human volunteer study which contained individual time-course exposure and urine biomarker data (Greer et al. 2002); thus it provided sufficient information for us to compare these two collection methods using the PBPK model. Spot urines were simulated as a second void at post-exposure day 1 to mimic the random spot urine sample collection in a population-based biomonitoring study. Even with the approximate time and volume of each void known (which is typically unknown in a population-based biomonitoring study); the model was not able to precisely predict a spot urine concentration for subjects in the Greer study at the lowest dose (Figure 4). Our results indicate that, for individuals, a 24 h (or longer) cumulative urine sample would provide a more precise intake estimate than a spot urine sample.

For urinary biomarker measurements, results are often expressed in terms of volume-weighted concentrations (*e.g.*, μg/L) or creatinine-normalized concentrations (*e.g.*, μg/g creatinine). Volume-weighted concentrations are influenced by urine dilution, and this variation is often addressed using creatinine normalization. In our analysis, the comparison between measurements and predictions was made for creatinine-normalized perchlorate concentrations, assuming that creatinine production is fixed for a given individual (Mage et al. 2004). This assumption, however, could introduce another source of uncertainty due to the considerable intra-individual daily variation (Greenblatt et al. 1976). For example, Fortin and colleagues observed up to 6.6 fold variation in the creatinine excretion rate over a 24 h period (Fortin et al. 2008).

In the current study, a human PBPK model was used to link dietary exposures to urinary perchlorate concentrations. While a PBPK model is more complex than a classical pharmacokinetic model (such as (Lorber 2009)), a PBPK model has the capability to simulate the time-course concentration of a biomarker in any intended tissue/fluid, at any given intake dose, from all aggregate sources and routes. Thus, the use of biomonitoring data with a PBPK model could be used to examine the impact of timing between exposure events and biomarker sample collection. This timing concern is especially important for a chemical such as perchlorate that has a half-life of approximately 7.5 h, where the biomarker measurement mainly reflects recent exposure (*e.g.*, perchlorate in last meal eaten) rather than exposure over the previous day, a time period on the order of several half-lives prior to sampling.

Furthermore, a PBPK model has the capability to predict target tissue dose, or even effects on biological processes when it is linked to a pharmacodynamic model. For example, the perchlorate model (Clewell et al. 2007) can predict not only perchlorate concentrations in urine, but also iodide uptake inhibition in different sub-populations: adults, children, pregnant and lactating women, fetus, and nursing infants. This capability will allow for future analyses on biomonitoring data collected from sensitive populations, and in other biological media. For example, Kirk and colleagues measured perchlorate from 36 breast milk samples from 18 states (Kirk et al. 2005). Pearce and colleagues detected perchlorate in all urine and breast milk samples from 57 lactating women (Pearce et al. 2007). Blount and colleagues measured perchlorate concentrations in maternal urine/serum, core serum, and amniotic fluid collected during cesarean-section surgeries on 150 women (Blount et al. 2009). Although a well-calibrated compartmental model can also be used to simulate the time-course of urinary perchlorate concentrations (Lorber 2009), its use for life-stage or target tissue simulations is limited.

In summary, by mapping the analytical results from the TDS and the NHANES 24-h dietary recall data, a PBPK model was able to predict a distribution of urinary perchlorate concentrations that was similar to

the distribution of measured urinary concentrations for the general population. This approach, however, was less successful at linking intake doses to biomarker measurements for individuals. Challenges and uncertainties that limited our capability to make this linkage were identified in the current study. Additional information on the geographical variation in the environmental concentrations, temporal profiles of human activities, as well as the selection of biomarkers based on chemical-specific pharmacokinetics, could increase our capability to estimate intake doses for individuals. Individual-level exposure assessment could assist in identifying whether the highest biomarker levels result from high-dose exposure events/activities or difference in pharmacokinetics (*e.g.*, less clearance capability).

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*Conflict of interest*

*No conflict of interest was declared.*

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**Table 1**: Example of (a) 24-h dietary recall data from NHANES 2001-2002, and (b) aggregate exposure dose profile for a female subject (corresponded to Figure 4).

(a) 24-hr dietary recall data

| ID | Time of eating | Gram weight of food consumed | Survey food code |
|---|---|---|---|
| 17164 | 7:00 | 187 | 61210620 |
| 17164 | 7:00 | 53 | 51180040 |
| 17164 | 7:00 | 5 | 14420200 |
| 17164 | 12:00 | 43 | 71401030 |
| 17164 | 12:00 | 43 | 51150000 |
| 17164 | 12:00 | 85 | 21500100 |
| 17164 | 12:00 | 14 | 75117020 |
| 17164 | 12:00 | 8 | 75113000 |
| 17164 | 12:00 | 15 | 74101000 |
| 17164 | 14:00 | 355 | 92410520 |
| 17164 | 17:30 | 290 | 63203010 |
| 17164 | 19:30 | 127 | 53342000 |
| 17164 | 19:30 | 98 | 58106720 |
| 17164 | 22:30 | 245 | 11113000 |

(b) Exposure Dose Profile

| ID | Time | Perchlorate Dose [ug] |
|---|---|---|
| 17164 | 7:00 | 1.87 |
| 17164 | 12:00 | 2.05 |
| 17164 | 14:00 | 0.22 |
| 17164 | 17:30 | 0.29 |
| 17164 | 19:30 | 1.03 |
| 17164 | 22:30 | 1.72 |

**Table 2**: Means, standard deviations, and selected percentiles of predicted and measured creatinine-normalized perchlorate concentrations (μg/g creatinine) for 340 non-pregnant women, age 15 – 45, from NHANES 2001-2002.

| | Mean | SD | 5th | 25th | 50th | 75th | 95th |
|---|---|---|---|---|---|---|---|
| Predicted | 2.78 | 2.44 | 0.42 | 1.18 | 2.03 | 3.61 | 7.55 |
| Measured | 3.42 | 3.25 | 0.88 | 1.61 | 2.58 | 3.98 | 8.88 |

**Table 3**: Correlations between age, body weight, amount of drinking water consumed, total dietary intake of perchlorate, measured perchlorate concentrations in urine (μg/L), measured creatinine-normalized perchlorate concentrations in urine (μg/g creatinine), PBPK-predicted creatinine-normalized perchlorate concentrations in urine (μg/g creatinine).

| 340 non-pregnant women, age 15 – 44, who were fasting on the day of urine collection | | | | |
|---|---|---|---|---|
| | Perc/Urine Data | PercIntake Estimation | Perc/Creatinine Data | Perc/Creatinine Prediction |
| Perc/Urine Data | — | | | |
| PercIntake Estimation | 0.08 | — | | |
| Perc/Creatinine Data | 0.66 | 0.16 | — | |
| Perc/Creatinine prediction | 0.08 | 0.82 | 0.20 | — |
| | | | | |
| 79 women who reported to be "milk drinker" and reported consuming milk in their 24-h dietary recall | | | | |
| | Perc/Urine Data | PercIntake Estimation | Perc/Creatinine Data | Perc/Creatinine Prediction |
| Perc/Urine Data | — | | | |
| PercIntake Estimation | -0.06 | — | | |
| Perc/Creatinine Data | 0.67 | 0.19 | — | |
| Perc/Creatinine prediction | -0.06 | 0.82 | 0.19 | — |
| | | | | |
| 212 women from whom urine samples were collected in the morning session | | | | |
| | Perc/Urine Data | PercIntake Estimation | Perc/Creatinine Data | Perc/Creatinine Prediction |
| Perc/Urine Data | — | | | |
| PercIntake Estimation | 0.09 | — | | |
| Perc/Creatinine Data | 0.68 | 0.22 | — | |
| Perc/Creatinine prediction | 0.12 | 0.84 | 0.23 | — |

Perc/UrineData : Measured perchlorate concentrations in urine (μg/L)

PercIntake Estimation: Total dietary intake of perchlorate (μg perchlorate in 24 h) estimated from perchlorate concentrations in food (TDS results) and NHANES 24-h dietary recall.

Perc/Creatin Data : Creatinine-normalized perchlorate concentrations in urine (μg/g creatinine)

Perc/Creatinine Prediction: PBPK model-predicted creatinine-normalized perchlorate concentration in urine (μg/g creatinine)