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Drinking water contribution to aggregate perchlorate intake of reproductive-age women in the United States estimated by dietary intake simulation and analysis of urinary excretion data

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Estimates of perchlorate intake by the US population can be derived from either urinary excretion data or through simulation of dietary intake. Estimates from surveys of urinary excretion (NHANES) are subject to substantial uncertainty owing to the small numbers of subjects for which data are currently available. In addition, current excretion estimates are derived from ''spot'' urine samples and include a component of short-term (intra-day) variability that may give biased estimates of the variability in average daily intakes. Previous dietary estimates have generally not included any contribution from drinking water, owing to a lack of data related to perchlorate concentrations in water supplies. In this paper, we derive simulation (Monte Carlo) estimates of dietary perchlorate intake distributions for reproductive-age women, which include explicit contributions from drinking water, and compare them to estimates based on urinary excretion. Perchlorate concentrations in water were estimated based on measurements from the US Environmental Protection Agency's UCMR1 database, and from other regional studies of perchlorate contamination. We find that including the drinking water contributions in the dietary simulations yields increases in the population's geometric mean perchlorate intake of 3–8 percent, with a conservative maximum of about 24 percent, compared to intakes estimated based on food intake alone. The intake distributions estimated from dietary and water consumption were found to be very similar to estimates based on creatinine-adjusted perchlorate excretion data from the NHANES, except for having lower population variability. When the dietary simulation data were adjusted to include a contribution from short-term variability similar to that in the ''spot'' urine samples, the variability in the NHANES and diet-derived estimates were found to be very similar. Our analyses indicate that a reasonable upper-bound estimate for the 95th percentile perchlorate intake among women of reproductive age in the US is on the order of 1.5×10^{-4} mg/kg/day.
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Introduction

Perchlorate (ClO_4^-) is known to affect thyroid function by interfering competitively with the thyroid sodium–iodine symporter (NIS) *in vitro* and after moderate to high acute doses *in vivo* (Dohan and Carrasco, 2003; Tonacchera et al., 2004). However, there is considerable uncertainty concerning the impacts of low-level chronic perchlorate exposures on human health. In 2005, the National Research Council (NRC) recommended that a reference dose (RfD) of 0.0007 mg/kg/day be established to protect sensitive human populations against adverse effects on thyroid function (NRC, 2005). Subsequently, the US Environmental Protection Agency (EPA) has adopted this recommendation in its Integrated Risk Information System database (U.S. EPA, 2005).

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Both NRC and EPA identified the fetuses of perchlorate-exposed mothers, as well as newborns and nursing infants, as the populations most sensitive to perchlorate exposure. The effect of reduced thyroid function on fetal development appears to be the most severe during the first trimester of pregnancy (Kooistra et al., 2006; Morreal de Escobar et al., 2007). Even relatively modest reductions in thyroid hormone levels in early pregnancy may be associated with adverse effects on fetal nervous system (Pop et al., 1999, 2003; Kooistra et al., 2006). For these reasons, this analysis focuses on estimating the contribution of drinking water to total perchlorate exposures received by reproductive-age women in the United States (18–45 years old), likely the most sensitive demographic group for which exposure data are available. U.S. EPA (2008c) has recently issued an interim health assessment recommending a maximum drinking water perchlorate level of 15 μg/l.

Despite the concern over perchlorate in water, the contribution of drinking water to the total US adult population perchlorate intake is not well-characterized, owing to limitations in the data related to both perchlorate levels in foods and in drinking water. In this paper, we

attempt to characterize the contribution of drinking water perchlorate contamination to the total perchlorate intake of reproductive-age women in the United States. The approach first involves analyzing the available data on perchlorate concentrations in drinking water from EPA's Phase 1 UCMR1 and other sources, to derive plausible estimates of the national distribution of perchlorate concentrations in the drinking water sources that are below detection or reporting limits in existing surveys. Second, we employ Monte Carlo simulation to incorporate these distributions into a total population exposure assessment, along with data related to dietary intake from perchlorate food sampling conducted by the US Food and Drug Administration (FDA). Finally, we compare our results to estimates of perchlorate intake by reproductive-age women derived from the NHANES urinary excretion data gathered in 2001–2004, adjusted for the effect of short-term (intra-day) variability in excretion rates.

Methods

Perchlorate Concentrations in Drinking Water

The largest and most representative set of data from public water supplies has been assembled by EPA under the first Unregulated Contaminants Monitoring Rule (UCMR1, U.S. EPA, 1999a). Under the original UCMR sampling strategy all "Large" and "Very Large" water systems (Systems sampled included all community water systems and all non-transient non-community water systems. A non-transient non-community system is "A public water system that regularly supplies water to at least 25 of the same people at least six months per year, but not year-round. Some examples are schools, factories, office buildings, and hospitals which have their own water systems.") (systems serving more than 10,000 customers), and a stratified random sample of 800 smaller systems, were required to perform "Assessment Sampling." Two to four samples were taken from each active entry point into the distribution system and smaller numbers of samples were taken from other locations (e.g., source water bodies, sampling points within the distribution system) at some systems. At the time the UCMR1 was initiated, large systems accounted for about 3.5 percent of the total community water systems, but served approximately 87 percent of the total customers (U.S. EPA, 1999b). Thus, despite the fact that only a small proportion of small systems were sampled, the UCMR1 database provides good coverage of drinking water perchlorate for systems serving the bulk of US water consumers. Perchlorate sampling was conducted during the years 2000–2006, with the majority of the samples taken from 2001 to 2005. The most recent version of the UCMR1 database includes 23,319 samples from 9663 entry points from 3417 systems in 50 states, the District of Columbia, Virgin Islands, Guam, and overseas military bases (U.S. EPA, 2008a). The UCMR1 does not include any data from private wells.

Although UCMR1 coverage is relatively good, the utility of the UCMR1 data for national exposure assessment is limited by a relatively high Method-Reporting Limit (MRL) of 4 μg/l specified for perchlorate analysis. This MRL corresponds to a drinking perchlorate water intake not far below the RfD ($\sim 1.0 \times 10^{-4}$ mg/kg/day, assuming a daily water intake of 1.4 l/day by a woman weighing 65 kg). In addition, the high reporting limit makes it impossible to accurately assess the frequency of low-level, sporadic perchlorate contamination.

Nationally, perchlorate was detected in 1.5% of all UCMR1 samples (348 out of 23,313 samples) and detected at least once in about 2.4 percent of all entry points sampled (230 out of 9663, see Table 1). Perchlorate was most frequently found in community water sources in Nevada, California, Oklahoma and New York where it was detected at least once in 16%, 12.9%, 10.2% and 10.0% of the entry points sampled, respectively. Detection frequencies were lower in other states, and perchlorate was not detected in any samples from 25 states, the District of Columbia, or the Virgin Islands.

Table 1. Perchlorate detection frequencies by entry point in the UCMR1 data (U.S. EPA, 2008a).

State	Systems sampled	Entry points sampled	Entry points with $ClO_4 > MRL$[a]	Frequency (%)
NV	7	25	4	16.0
CA	170	577	74	12.9
NY	128	321	32	10.0
OK	52	98	10	10.2
WA	72	284	15	5.3
NC	113	391	14	3.6
OH	147	182	8	4.4
MD	34	57	3	5.3
AZ	49	467	12	2.6
NE	17	63	1	1.6
AR	46	82	3	3.7
SC	54	99	3	3.0
NJ	126	471	7	1.5
NM	24	107	1	0.9
FL	233	575	9	1.6
AL	97	322	5	1.6
PA	154	423	9	2.1
GA	99	228	3	1.3
MN	83	214	2	0.9
VA	50	89	1	1.1
TX	250	800	5	0.6
IL	132	320	2	0.6
LA	85	272	1	0.4
MS	70	271	1	0.4
TN	104	148	1	0.7
PR	87	301	1	0.3
MA	121	440	1	0.2
25 States	798	1929	0	0.0
Total	3417	9663	230	2.4

[a]One or more detections; Method-Reporting Limit (MRL) = 4 μg/l.

Because of the very low detection frequency in the UCMR1 data, it is difficult to assess the national distribution of perchlorate concentrations below 4 μg/l. Conventional parametric methods for fitting censored data, along with bootstrap and other numerical methods are of limited use in estimating the distribution of perchlorate concentration in the approximately 97.5% of entry points where perchlorate was not detected. In the absence of data from the UCMR1 itself, we have used simple approximations to span what we believe to be a reasonable range of ''background'' perchlorate concentrations that were not detected in the UCMR1. These estimates are informed by the results of other surveys discussed below, which have employed more sensitive analytical methods.

A number of studies support the idea that low-level perchlorate contamination is relatively widespread, occurring even far from large industrial releases. This contamination can arise from natural sources (Rajagopalan et al., 2006; Rao et al., 2007), diffuse releases from fertilizer use (Dasgupta et al., 2006; Rice et al., 2007), and localized contamination from explosives and fireworks (MDEP, 2006). Jackson et al. (2004) found groundwater perchlorate concentrations greater than 0.5 μg/l in 46% of wells in west Texas and New Mexico. Rajagopalan et al. (2006), sampling in the same area, reported groundwater perchlorate concentrations between 0.1 μg/l and 4 μg/l in 35% of wells. Data from Massachusetts (MDEP, 2006) and Maryland (Rice et al., 2007), as well as infrequent detections in the UMCR1 data for many states at locations distant from known perchlorate releases, likewise suggest that low-level perchlorate contamination may be common, if not ubiquitous, in drinking water.

For our exposure assessment, we have derived three sets of estimated national drinking water perchlorate distributions (distributions 1, 2, and 3). These distributions are intended to span a credible range of exposures for reproductive-age women in the US, including those residing in areas with documented drinking water contamination. U.S. EPA (2008b) have recently derived drinking water exposure estimates based on the UCMR data, using different methods, which again, do not account for contributions of low-level background exposures to the national intake distribution.

Distribution 1 is based on the UCMR1 monitoring results without any added ''background.'' Perchlorate concentration data for this distribution came from the 23,319 ''EP'' (entry point) samples included in the 2008 UCMR1 data release (U.S. EPA, 2008a). Samples from source waters and samples taken within the distribution systems were excluded to avoid double counting of exposed populations. Where an entry point was sampled more than once and perchlorate was detected at least once, the arithmetic mean perchlorate concentration was calculated, with non-detect samples at that entry point being counted as values equal to one-half the MRL, or 2 μg/l. (Generally, we found little evidence of high variability within entry-point concentrations that would suggest lognormality). Where perchlorate was never detected at a sampled entry point, an average perchlorate concentration of zero was assigned under Distribution 1.

Each entry point was then assigned a population weight, corresponding to the estimated number of customers served. The population weights were assigned based on national statistics related to the total populations served by community water systems in different size categories and the average number of entry points for each system size category (U.S. EPA, 2004a; U.S. EPA, 1999b). Each member of the ''Very Large'', ''Large'', ''Medium'', ''Small'', and ''Very Small'' categories were assumed to serve the same number of customers, and assumed to have the same number of entry points. This approach was necessary because detailed data on the number of active entry points or populations served are not available for the individual water systems sampled in the UCMR1. The cumulative perchlorate exposure concentration distribution was then generated by sorting the EP perchlorate concentrations, with their corresponding population weights, in ascending order. The resulting population-weighted perchlorate distribution is summarized in the left-hand column of Table 2.

It can be seen that consistent with the raw data, the bulk of the population in Distribution 1 is assigned a perchlorate drinking water concentration of zero, with exposure concentrations greater than zero assigned only to the upper 2.6 percent of the population whose entry points had at least one perchlorate detection above the MRL. The assumption of zero exposure for such a large proportion of the population will almost certainly result in underestimation of total population exposures. Distribution 1 is best interpreted as a low-end estimate against which the other distributions can be compared.

Hypothetical drinking water perchlorate Distributions 2 and 3 differ from Distribution 1 in that ''background'' low-level perchlorate exposures were assigned to different proportions of the entry points with all below-MRL

Table 2. National drinking water perchlorate distributions derived from UCMR1 sampling, with low-level background exposures substituted for non-detect values

Population-weighted percentile, μg/l	Drinking water distribution number		
	1	2	3
Maximum	107	107	107
99%	5.6	5.6	5.6
98%	3.7	3.7	3.7
95%	0	0.5	2
90%	0	0.3	1
75%	0	0.1	0.5
50%	0	0.1	0.5
25%	0	0	0.2
Minimum	0	0	0

perchlorate analytical results. Entry points with no results above the MRL were assigned a range of perchlorate concentrations, approximating the assumed distribution of low-level, undetected ''background'' perchlorate contamination. Under Distribution 2, entry points with one or more ''detect'' concentrations were assigned the same concentration as under Distribution 1. Estimated perchlorate concentrations for below-MRL entry points were ''tapered'' from 3.7 μg/l at the 98th percentile to 0.5 μg/l at the 95th percentile of population exposure, and down to 0.1 μg/l at the 50th percentile. The remaining entry points were assigned a perchlorate concentration of zero under Distribution 2.

Distribution 3 is similar to Distribution 2, except that perchlorate concentrations in the non-detect entry points are assigned higher values (Table 2). Under distribution 3, the 95th percentile entry point is assigned a perchlorate concentration of 2.0 μg/l, tapering to 0.2 μg/l for the 25th percentile. Both Distribution 2 and Distribution 3 incorporate assumptions concerning low-level ''background'' perchlorate distribution in drinking water that are generally consistent with the previously cited studies of Jackson et al. (2004), Rajagopalan et al. (2006), and Rao et al., 2007, with Distribution 3 assuming more widespread occurrence than Distribution 2.

Food and Water Consumption Data

The US Department of Agriculture's (USDA) Continuing Survey of Food Intake by Individuals (CSFII) from 1994 to 1996 and 1998 provided data that were used to estimate the food and water intake distributions used in this analysis (USDA, 2008). The CSFII surveys employed a stratified area probability sample of individuals living in the US, using 24-h recall questionnaires to collect consumption data on two non-consecutive days. Data were collected on 20,607 individuals living in the 50 United States and the District of Columbia. Surveys collected information on the raw and prepared food consumption, and USDA subsequently converted these foods into raw agricultural commodities using recipe data also from the CSFII.

The 1994–1996 and 1998 CSFII surveys also collected information about the distribution of water consumption. ''Direct'' water consumption was defined to include water consumed as-is from community water systems (i.e., tap water), individual wells, or bottled water. ''Indirect'' water consumption includes water consumed in prepared foods or beverages. In this analysis, direct and indirect water coming from ''public water systems'' is assumed to be contaminated with perchlorate, whereas water from other sources (bottled, for example) is not included. Table 3 summarizes the estimated distribution of direct and indirect water consumption from public water systems, for women aged 20 years and above (U.S. EPA, 2004b), that were used in the perchlorate intake dietary simulation. The estimated median water intake for an adult woman from the survey is 13 ml/kg/day, corresponding to approximately 845 ml/day for a woman weighing 65 kg. The estimated mean water intake for an adult woman is 16 ml/kg/day, or about 1040 ml/day. The median water intake for reproductive-age women calculated from the NHANES data (see results) is 885 ml/day, close to the value derived from the CSFII.

Table 3. Estimated community water consumption rates of women 20 years and older, ml/kg body weight-day, (USDA, 2008).

Percentile	Direct (ml/kg/d)	Indirect (ml/kg/d)	Direct and indirect combined (ml/kg/d)
Mean	8	8	16
1st	0	0	0
5th	0	0	0
10th	0	0	1
25th	0	2	6
Median	5	6	13
75th	12	11	22
90th	21	17	33
95th	27	22	40
99th	47	37	62

Perchlorate Concentrations in Food

Perchlorate concentrations in foods were estimated based on results from the FDA's 2004–2005 Exploratory Survey Data on Perchlorate in Food (U.S. FDA, 2007). FDA analyzed 770 samples of 33 foods and beverages, including milk, fruits and fruit juices, vegetables, grain products, seafood, and bottled water. Domestic produce samples were collected at the grower or at packing sheds, whereas fruit juices, imported produce samples, and grains were collected at retail establishments. The exploratory sampling included only raw produce, and not prepared foods. Detection limits in this survey ranged from 0.3 to 1.0 ug/kg. Perchlorate was detected in 607 of 770 samples (79%), and the mean perchlorate concentration ranged from below detection limits (five products) to 116 ug/kg (spinach).

FDA's exploratory perchlorate sampling data were used in this analysis because the raw data related to contaminant concentration distributions were available. In 2005 and 2006, FDA analyzed a larger variety of foods collected in market-based surveys for perchlorate contamination (U.S. FDA, 2008). However, individual sample data from those surveys were not available at the time of this analysis. The 2004 and 2005 exploratory data sets allowed for the use of Monte Carlo simulation methods that capture, at least to some extent, exposure variability among women of childbearing age in the United States. The limitations of these data are discussed in more detail below.

Dietary, Water Perchlorate Intake Estimation Approach

LifeLine Software, Version 5.0.1, (Price and Chaisson, 2005; LifeLine, 2007) was used to estimate perchlorate intake from foods and tap water. The LifeLine exposure model is a

probabilistic tool that uses Monte Carlo sampling to estimate distributions of individual exposures to chemicals from multiple sources (Price and Chaisson, 2005). As noted previously, LifeLine uses food and water consumption data from the CSFII 1994–1996 and 1998 surveys, along with perchlorate concentration data in raw commodities, to estimate dietary intakes. As part of the simulation, the model translates raw commodities into ''as-eaten'' foods, using recipes derived from the CSFII surveys. Concentrations of perchlorate in foods as they are eaten may be diluted by ingredients that are not contaminated by perchlorate. In this analysis, a ''processing factor'' value of 1.0 was employed, meaning that perchlorate was assumed to persist during all forms of preparation.

For purposes of this analysis, individual exposures were estimated for a population of 10,000 women in each perchlorate exposure scenario. Population-weighted average exposure percentiles for 20-, 30-, and 40-year-old women (U.S. Census 2000) were calculated for each scenario to estimate the distributions of perchlorate intake by reproductive-age women.

Perchlorate Intake Estimates Based on NHANES Urinary Excretion Data

As discussed earlier, perchlorate urinary excretion data were collected as part of the NHANES survey. Results from the 2001–2002 cohort have been available for some time, but data for the 2003 cohort were released only recently (NCHS, 2008). The 2003–2004 dataset contains perchlorate analytical results for 2522 subjects, 454 of whom were reproductive-age women. This is comparable in size to the 2001–2002 dataset, which included perchlorate data for 2820 subjects, 471 of whom were reproductive-age women.

In this analysis, we have estimated perchlorate intake distributions from the NHANES data in a manner similar to that employed by Blount et al. (2006) in analyzing the 2001–2002 data. Differences in our approach include: (1) we have estimated distributions for reproductive-age women instead of for all adult females, and (2) we have used an updated approach to adjust for differences in 24-h creatinine excretion which takes into account racial differences in excretion rates (Mage et al., 2008). In addition, we have generated two separate estimates of perchlorate intake, one based on the 2001–2002 data previously analyzed by Blount et al. (2006) and another based on data from the 2003–2004 sampling rounds. In calculating these statistics, the NHANES survey weights were used; thus the derived distributions should correspond to the national distribution of perchlorate intake (within the limitations of the NHANES sampling scheme).

Adjustment of Dietary Intake Distributions to Include Short-Term Variability in Perchlorate Excretion

Intake distributions from the dietary simulation are not directly comparable to the intake distributions derived from the NHANES data, because the dietary estimation model outputs represent long-term daily (24-hour) average values, whereas the NHANES data include a contribution from intra-day variation in perchlorate excretion in ''spot'' urine samples. Thus, the variability in perchlorate intake estimates derived based on spot urine excretion is likely to be greater than the variability in intake derived from a dietary/water model for the same population. To illustrate, assume that both the individual perchlorate intake estimates from the simulation and derived from the NHANES data are log normally distributed. (See Figures 1 and 3). If μ and σ^2 represent the means and variance of log-transformed variables, respectively, then

$$\text{Log (daily dietary intake)} \sim \text{N}\,(\mu_{\text{DIET}}, \sigma^2_{\text{DIET}}) \quad (1)$$

and

$$\text{Log (daily NHANES intake)} \leftarrow \sim \text{N}\,(\mu_{\text{NHANES}}, \sigma^2_{\text{NHANES}}) \quad (2)$$

That is, the log of the simulated daily dietary intake is normally distributed with its own mean and variance derived from the daily simulation outputs. The log of the NHANES estimate is also log normally distributed. However, in the case of the NHANES data, the observed variance has two components, one being the long-term variation in perchlorate intake (analogous to that which is modeled in the dietary simulation), and the other being the contribution from intra-day variations in excretion (owing to fluctuations in hydration, urinary volume, etc.) that affect concentrations observed in the spot urine samples. That is:

$$\sigma^2_{\text{NHANES}} = \sigma^2_{\text{Long-term}} + \sigma^2_{\text{Intra-day}} \quad (3)$$

Thus, if we wish to compare the distributions of perchlorate intake derived from dietary sources with those based on the NHANES data, it is necessary to adjust for the intra-day variability in the latter set of estimates.

Unfortunately, neither the NHANES data nor the dietary exposure methodology provides information that allows direct estimation of the contribution of intra-day variability to the total NHANES intake variability. Similarly, we are unaware of any other epidemiological data that report the results of intra-day variability in perchlorate excretion. Such data are, however, available from the Greer et al. (2002) study from which the NRC derived their recommended RfD. Merrill (2001) provides data on urinary perchlorate concentrations and void volumes up to 14 days of uniform perchlorate dosing, for 20 subjects in Greer's ''main study.'' These subjects received daily perchlorate doses between 0.007 and 0.5 mg/kg/day in water (Greer et al. 2002). Measurements from the eighth through the fourteenth exposure days were used to assure that perchlorate intake and excretion were as close to steady-state equilibrium as possible. For most subjects, data were available for between two to eight voids per day for 2–3 days during this period. Data from

individual voids (mass of perchlorate excreted) were log-transformed, and the variance of the log of perchlorate excretion about the daily means log excretion values were calculated for use in characterizing the distribution of intra-day variability.

Results

Perchlorate Intake Estimates Based on Dietary Simulation and NHANES Urinary Excretion Data

Table 4 compares the perchlorate intake distributions resulting from the dietary simulations with those derived from the 2001–2002 and 2003–2004 NHANES urinary excretion data. Both the dietary simulation and urinary excretion estimates are described rather well by log normal distributions (Figure 1), but the variability in the urinary excretion-based estimates is larger than that seen in the simulation results. As discussed below, this is at least partially because the perchlorate intake estimates derived from the spot urine samples in the NHANES include a contribution from intra-day variability that is not included in the dietary simulation results.

Consistent with previous analyses, the estimated contribution from drinking water perchlorate in the dietary simulations is small to moderate. Median dietary intakes estimated using water Distributions 1, 2, and 3 were 5.7×10^{-5}, 5.9×10^{-5}, and 6.8×10^{-5} mg/kg/day, respectively, compared with the median intake estimate of 5.5×10^{-5} mg/kg/day derived solely from foods. These values correspond to 3%, 7%, and 24% increases relative to the baseline (food only) estimate. Increases in the upper (95th) percentiles associated with inclusion of drinking water perchlorate are similar to the increases in the central tendency estimates.

The geometric mean and median perchlorate intake estimates derived from the 2001–2002 NHANES data (5.7×10^{-5} and 5.6×10^{-5} mg/kg/day, respectively) are very similar to the estimates derived from the ''Foods Only'' dietary simulation, and those derived from the dietary simulations that include either water perchlorate Distribution 1 or Distribution 2. As noted above, the spread in the distribution of the NHANES estimates is considerably wider than that generated by the dietary simulations, and thus the lower and higher percentiles do not match well to the dietary simulation (Figure 1).

Interestingly, the perchlorate intake estimates derived from the 2003–2004 data are lower than those estimated from the 2001–2002 data. The median and geometric mean values from 2003–2004 measurements are 4.5×10^{-5} and 4.7×10^{-5} mg/kg/day, respectively, about 20 percent below the corresponding estimates for the earlier time period. Although the difference is statistically significant (Satterthwaite-adjusted χ^2 test applied to the stratified and weighted data, $P = 0.04$), it would be premature to infer a temporal trend in population perchlorate intake based on only two time periods.

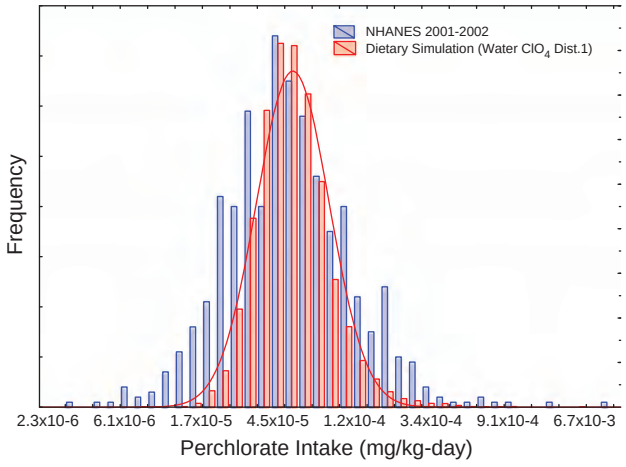

Figure 1. Comparison of estimated perchlorate intake distributions from dietary simulation and NHANES urinary excretion data (2001–2002) (a) Curves indicate best fitting log normal distributions (*x* axis has been log-transformed).

Table 4. Perchlorate intake distribution estimated dietary (food + water) simulations and from NHANES urinary excretion data (mg/kg/day).

Estimated percentiles, summary statistics	Foods only	Foods + water dist. 1	Foods + water dist. 2	Foods + water dist. 3	NHANES 2001–2002[a]	NHANES 2003–2004[a]
5th	2.9×10^{-5}	2.9×10^{-5}	3.1×10^{-5}	3.7×10^{-5}	1.7×10^{-5}	1.5×10^{-5}
10th	3.3×10^{-5}	3.4×10^{-5}	3.6×10^{-5}	4.2×10^{-5}	2.4×10^{-5}	2.0×10^{-5}
25th	4.2×10^{-5}	4.3×10^{-5}	4.5×10^{-5}	5.3×10^{-5}	3.5×10^{-5}	2.9×10^{-5}
Median	5.5×10^{-5}	5.7×10^{-5}	5.9×10^{-5}	6.8×10^{-5}	5.6×10^{-5}	4.5×10^{-5}
75th	7.3×10^{-5}	7.6×10^{-5}	7.9×10^{-5}	9.0×10^{-5}	9.0×10^{-5}	7.2×10^{-5}
90th	9.7×10^{-5}	1.0×10^{-4}	1.1×10^{-4}	1.2×10^{-4}	1.5×10^{-5}	1.3×10^{-5}
95th	1.2×10^{-4}	1.3×10^{-4}	1.4×10^{-4}	1.5×10^{-4}	2.1×10^{-5}	1.9×10^{-5}
Arithmetic Mean	6.3×10^{-5}	6.7×10^{-5}	7.1×10^{-5}	8.1×10^{-5}	9.2×10^{-5}	6.9×10^{-5}
Geometric Mean	5.6×10^{-5}	5.9×10^{-5}	6.1×10^{-5}	7.3×10^{-5}	5.7×10^{-5}	4.7×10^{-5}
Geom. SD	1.56	1.60	1.60	1.54	2.25	2.18

[a]Values derived from weighted data for 15 to 45 year olds.

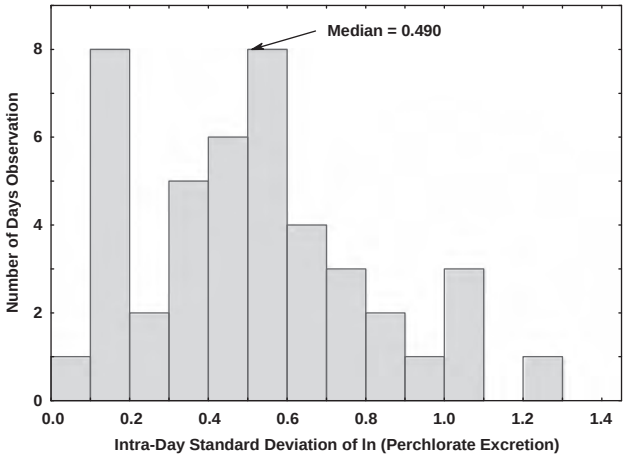

Figure 2. Distribution of intra-day variability in perchlorate excretion (Greer et al., 2002).

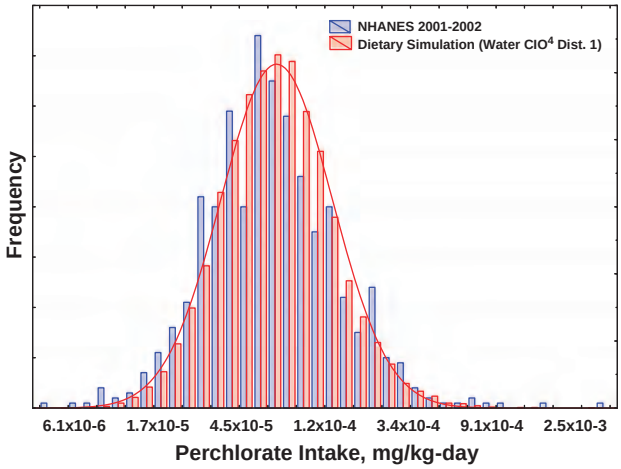

Figure 3. Comparison of estimated perchlorate intake distributions from dietary simulation with added intra-day variability and NHANES urinary excretion data (2001–2002). (a) Curves indicate best fitting log normal distributions (*x* axis has been log-transformed).

Accounting for Intra-Day Variability in Perchlorate Excretion

As discussed earlier, a major reason for the difference in the observed variability in perchlorate intake distributions from dietary studies and those derived from the NHANES data arise because the NHANES excretion estimates include a contribution from intra-day variability in the spot urine samples. Figure 2 shows the intra-day variability in perchlorate excretion results underlying the Greer et al. (2002) human volunteer study (Merrill, 2001). For each day of observations, data on multiple voids were used to calculate the variability of perchlorate excretion about the mean excretion per void. Probability plots of intra-day variability in pooled perchlorate excretion data from individual subjects (data not shown) were generally consistent with log normality. The results in Figure 2 are presented in the form of the SD of the natural logarithms of perchlorate excretion during each of 44 days of observation in 19 subjects from which usable data were obtained. It can be seen that the data are highly variable with a median intra-day log SD of 0.49 (mean = 0.51).

Distribution of Intra-Day Variability in Perchlorate Excretion

These results were used to investigate the extent to which the intra-day variability explains the observed differences between the dietary simulation results and the perchlorate intake distributions seen in the NHANES data (Figure 2) (Greer et al., 2002). To address this question, a simulation was performed in which a component corresponding to intra-day variability was added to the dietary simulation results, that is, random values distributed as N (0, 0.51) were added to the logarithms of each of the 10,000 iterations from the dietary simulation for women exposed to drinking water Distribution 1, and the result converted back to mg/kg/day. The results are summarized in Figure 3.

It can be seen that the addition of the intra-day variability estimated from the Greer et al. (2002) data to the dietary simulation results (including water perchlorate Distribution 1) produces an intake distribution that is very similar to the distribution derived from the NHANES 2001–2002 urinary excretion data. With the added variability, the dietary intake results (including perchlorate water Distribution 1) are well described by a log normal distribution with a geometric SD of 1.99, compared with the GSD of 2.25 for the NHANES data. Similar results are obtained when the intra-day variability is added into the results of the other dietary simulations.

Discussion

Consistent with findings from previous studies or perchlorate concentrations in foods (Jackson et al., 2005; Sanchez et al., 2005a; Sanchez et al., 2005b; Murray et al., 2008; Sanchez et al., 2008), results from our dietary simulations suggest that drinking water contamination accounts for a relatively small proportion of total population intake for reproductive-age women in the United States. As shown in Table 5, addition of reasonable assumed drinking water perchlorate distributions increases the central tendency (mean and median) estimates of national perchlorate intakes for reproductive-age women by between approximately 3 and 24%.

Results from our dietary simulations are generally consistent with the more recent estimates based on food concentrations and dietary composition patterns (Table 5). Sanchez et al. (2008) also used Monte Carlo analysis to estimate the perchlorate intake distribution for women aged

Table 5. Comparison of recent estimates of perchlorate intake by reproductive-age women in the United States.

Study	Population	Exposure sources	Estimation method	Arithmetic mean perchlorate intake, mg/kg/day	90th percentile perchlorate intake, mg/kg/day
Sanchez *et al.* (2008)	Females, age 15–45 years	Fruits, vegetables, milk	Dietary simulation (US)	4.1×10^{-5}	7.0×10^{-5}
			Dietary, deterministic (US)	2.9×10^{-5}	6.3×10^{-5}
			Dietary, deterministic (LCRR)	6.7×10^{-5}	1.3×10^{-4}
Murray *et al.* (2008)	Females, 25–30 years	Fruits, vegetables, grain, dairy products, meat, poultry, prepared foods (U.S. FDA TDS)	Dietary, deterministic	9.0×10^{-5} [a]	1.1×10^{-4} [a]
U.S. EPA (2008b)	Females, age 15–44 years (Group I)[b]	Total	NHANES urinary excretion data	8.1×10^{-5}	1.4×10^{-4}
	Females, age 15–44 years (Group III)[b]			9.3×10^{-5}	1.4×10^{-4}
This analysis	Females 15–45 (diet only)	Fruits, vegetables, dairy	Dietary simulation	6.4×10^{-5}	9.7×10^{-5}
	Females, age 15–45 years (H_2O Dist. 1)	Fruits, vegetables, dairy, drinking water		6.7×10^{-5}	1.0×10^{-4}
	Females, age 15–45 years (H_2O Dist. 2)			7.1×10^{-5}	1.1×10^{-4}
	Females, age 15–45 years (H_2O Dist. 3)			7.9×10^{-5}	1.2×10^{-5}

LCRR, lower Colorado river region; TDS, total dietary survey.
[a]Displayed values are lower and upper bounds on the mean intake, calculated with ''nondetect'' values counted as zero and at detection limits, respectively.
[b]Bin I, Bin III = subjects more/less likely to be exposed to perchlorate in drinking water, respectively (see text).

between 13 and 49 years based on perchlorate concentration data from samples of 25 fruits and vegetables, as well as dairy milk, from the lower Colorado River region. When they assumed that women would consume only produce grown in the region, they estimated a mean perchlorate intake of 6.7×10^{-5} mg/kg/day and a 90th percentile intake of 1.3×10^{-4} mg/kg/day. When they assumed that the perchlorate levels in produce were diluted with uncontaminated produce from outside the lower Colorado River region, they estimated mean and 90th percentile intakes of 2.9×10^{-5} and 6.3×10^{-5} mg/kg/day, respectively. The former estimates are very close to our mean and 90th percentile intake estimates of 6.3×10^{-5} and 1.2×10^{-4} mg/kg/day for dietary consumption, including dairy products.

Murray et al. (2008) derived point estimates of national perchlorate intake by reproductive-age women and other groups based on data from the most recent (2005–2006) Total Dietary Survey perchlorate concentration data and consumption amounts from the 1996–1998 CSFII. They estimated ''lower-bound'' and ''upper-bound'' mean perchlorate intakes for women aged between 25 to 45 years to be 9×10^{-5} and 1.1×10^{-4} mg/kg/day. Because these estimates are based on the product of arithmetic average food concentrations and arithmetic average food consumption, both of which are likely to be positively skewed, they are not directly comparable to the mean and percentile values calculated in our analyses, and they should best be viewed as conservative central tendency values. Even so, these estimates are not very different from our results for food-alone perchlorate intake.

Although the results of the dietary simulations suggest that drinking water contributes relatively little to population intake, the estimates of upper percentiles of distribution, representing the most heavily exposed subgroups, are highly uncertain. In addition, the dietary studies do not have sufficient resolution to allow identification of specific regional and ethnic subpopulations that may be receiving the highest exposures, nor does it incorporate potential regional correlations between food and water perchlorate concentrations. As noted previously, the dietary exposure simulation also does not include the portion of the population obtaining water from private wells.

The NHANES urinary excretion data also shed light on the distribution of perchlorate intake in reproductive-age women. In addition to the previous dietary-based estimates, U.S. EPA (2008b) sponsored an analysis of the NHANES 2001–2002 urinary excretion data coupled to the UCMR1 drinking water monitoring results. Subjects were ''binned'' into three strata corresponding to their likelihood of exposure to perchlorate in drinking water, and the creatinine-adjusted distributions of perchlorate excretion were compared across the strata. Bin I included subjects who were judged to be more likely to have been exposed based on perchlorate detections in drinking water sources in their county of

residence. Subjects were categorized into Bin III when they were considered unlikely to have been exposed to perchlorate-contaminated drinking water. EPA found that the estimated perchlorate distributions for the 15- to 44-year-old women in Bins I and III were very similar, further supporting the relatively minor contribution of drinking water perchlorate to total population exposure. Although the calculated mean perchlorate intake is actually lower for Bin I than Bin III women (implying that the drinking water-exposed group actually had lower perchlorate intake), this may be in part due to the relatively small number of subjects in these strata (57 in Bin I, 505 in Bin III) and the low spatial resolution of the binning process (county level). When data for all 2382 subjects were analyzed, the estimated mean perchlorate intake for the Bin I subjects ($1.0x10^{-4}$ mg/kg/day) was approximately 11% higher than that for the Bin III subjects (9.0×10^{-5} mg/kg/day).

Results from the NHANES urinary excretion studies suggest that the upper percentile perchlorate intake estimates may approach levels of concern (90th percentile = 1.0–1.2×10^{-4} mg/kg/day) in relation to the current RfD. However, our analysis suggests that the differences between the population distributions of perchlorate intake estimated using dietary simulation and those based on NHANES urinary excretion data can be largely explained by the added short-term (intra-day) variability associated with the analysis of spot urine samples in the national survey. This suggests that analyses of the NHANES data without correction for intra-day variability may somewhat overestimate the variability in daily perchlorate intake in US reproductive-age women and, consequently, may overestimate the upper percentiles of the population distribution. However, the magnitude of potential bias in the estimates appears to be moderate; the 95th percentile estimate of perchlorate intake from the 2001–2002 NHANES data is only about 50 percent higher than the daily average value estimated from the dietary simulation.

Taken together, these results suggest that only a very small proportion of reproductive-age women in the United States are likely to receive daily average perchlorate intake from all sources (food and drinking water) greater than 7.0×10^{-4} mg/kg/day, EPA's RfD value. This does not necessarily imply that the perchlorate intake is not a health concern for some portion of the population, however small. Blount et al. (2007) observed an inverse relationship between perchlorate intake and serum T4 levels in iodine-deficient women among the 2001–2002 NHANES subjects, despite the fact that the great proportion of these women had perchlorate intakes (as measured by urinary excretion) well below the RfD. Steinmaus et al. (2007) observed an interaction of smoking status and perchlorate in the same NHANES cohort such that perchlorate impact on T4 levels was stronger in smokers than non-smokers, thus identifying another potential risk factor for adverse effects. Analyses of data from the 2007–2008 NHANES cohort will shed additional light on both the distribution of exposures and the strength of correlations between perchlorate exposure and indices of thyroid function in the general population (Blount et al., 2007).

Our analyses are subject to a number of limitations, including the fact that our estimates of national drinking water perchlorate distributions are highly uncertain owing to the paucity of data at detection limits below 4 ìg/l. Nonetheless, we believe that our three hypothetical distributions cover a reasonable range of perchlorate concentrations. All are consistent with the UCMR1 data in the extreme upper percentiles, and with data from other regional studies showing widespread lower-level contamination from natural sources or fertilizer use (Dasgupta et al., 2006; Rajagopalan et al., 2006; Plummer et al., 2006; Rao et al., 2007). Another limitation of our dietary simulation is that data on perchlorate concentrations in food from the FDA Exploratory Survey are not a random national sample, but were taken from locations where the likelihood of perchlorate contamination was suspected to be high. Based on comparisons to other dietary studies shown in Table 5; however, it does not appear that use of the inclusion of these data as estimates of the distribution of perchlorate in foods has seriously biased our results significantly compared with what would be expected if a full national sample was used.

With regard to our analyses of the potential impacts of intra-day variation on the NHANES-derived perchlorate intake distributions, we recognize that data on short-term variability are limited and come from a small sample of healthy volunteer adults (Merrill, 2001). These volunteers received metered daily perchlorate doses as part of a planned experimental protocol, and void volumes and perchlorate concentrations were carefully measured. The extent to which intra-day excretion variability might differ between the volunteer subjects and that seen in the spot urine samples from the NHANES subjects cannot be estimated. Our analyses show, however, that the variability seen in the volunteer study is useful for reconciling the results of dietary intake and urinary excretion studies.

Conflict of interest

The authors declare no conflict of interest.

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