Perchlorate Exposure of the US Population, 2001–2002

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Perchlorate is commonly found in the environment and can impair thyroid function at pharmacological doses. As a result of the potential for widespread human exposure to this biologically active chemical, we assessed perchlorate exposure in a nationally representative population of 2820 US residents, ages 6 years and older, during 2001 and 2002 as part of the National Health and Nutrition Examination Survey (NHANES). We found detectable levels of perchlorate ($>0.05\,\mu g/l$) in all 2820 urine samples tested, indicating widespread human exposure to perchlorate. Urinary perchlorate levels were distributed in a log normal fashion with a median of $3.6\,\mu g/l$ ($3.38\,\mu g/g$ creatinine) and a 95th percentile of $14\,\mu g/l$ ($12.7\,\mu g/g$ creatinine). When geometric means of urinary perchlorate levels were adjusted for age, fasting, sex and race-ethnicity, we found significantly higher levels of urinary perchlorate in children compared with adolescents and adults. We estimated total daily perchlorate dose for each adult (ages 20 years and older), based on urinary perchlorate, urinary creatinine concentration and physiological parameters predictive of creatinine excretion rate. The 95th percentile of the distribution of estimated daily perchlorate doses in the adult population was $0.234\,\mu g/kg$-day [CI 0.202–0.268 $\mu g/kg$-day] and is below the EPA reference dose ($0.7\,\mu g/$kg-day), a dose estimated to be without appreciable risk of adverse effects during a lifetime of exposure. These data provide the first population-based assessment of the magnitude and prevalence of perchlorate exposure in the US.
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Introduction

Perchlorate is an inorganic anion that is synthesized primarily as ammonium perchlorate for use as an oxidant in solid rocket propellant (Mendiratta et al., 1996). Perchlorate can also form naturally in the atmosphere (Dasgupta et al., 2005) leading to trace levels in precipitation and is concentrated geologically in some locations such as regions of west Texas (Dasgupta et al., 2005) and northern Chile (Urbansky et al., 2001). A combination of human activities and natural sources has led to the widespread presence of perchlorate in the environment. The US Environmental Protection Agency (EPA) included perchlorate on the Drinking Water Candidate Contaminant List and requires public water systems to monitor and report perchlorate in drinking water (EPA, 1998, 1999). As of November 2005, perchlorate was detected at least once in 4.1% of community drinking water systems from 26 different states and two territories, with levels ranging from the method detection limit of $4\,\mu g/l$ to a maximum at $420\,\mu g/l$ (EPA, 2005b). Perchlorate exposure from the diet is likely, due to the contamination of vegetable crops irrigated with perchlorate-containing water (Yu et al., 2004) or fertilized with Chilean nitrate (Urbansky et al., 2001). Milk can also contain perchlorate, possibly from perchlorate contamination of forage crops (Kirk et al., 2003; Capuco et al., 2005).

The prevalence of trace levels of perchlorate in the environment leads to human exposure. Environmental perchlorate exposure is of possible health concern because much larger doses of perchlorate have been shown to competitively inhibit iodide uptake by the thyroid gland (Wyngaarden et al., 1953; Greer et al., 2002); sustained inhibition of iodide uptake could potentially lead to hypothyroidism. The thyroid plays a crucial role in energy homeostasis and neurological development. Hypothyroidism can lead to metabolic problems in adults and abnormal development in children (Braverman and Utiger, 2000).

Useful human exposure data can be obtained by directly measuring levels of an environmental toxicant in the human body (i.e., biomonitoring) (Pirkle et al., 1995). Urinary perchlorate provides a reasonable measure of human exposure because 70–95% of a perchlorate dose is excreted unchanged in the urine with a half-life of $\sim 8\,h$ (Anbar et al., 1959; Lawrence et al., 2000; Greer et al., 2002). Sensitive and selective methods are needed to quantify perchlorate anion in urine in the presence of much higher levels of chloride, sulfate and phosphate anions. We recently developed a sensitive and

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[1]The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention

selective analytical method capable of quantifying perchlorate in human urine as low as 0.05 μg/l (Valentin-Blasini et al., 2005). In this paper, we have applied this method to measure perchlorate in urine samples collected from a representative sample of 2820 persons, aged 6 years and older, as part of the 2001–2002 National Health and Nutrition Examination Survey (NHANES).

Subjects and methods

Study Design

NHANES is conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC). This survey is designed to assess the health and nutrition status of the civilian, non-institutionalized US population (CDC, 2004). The sampling design for NHANES is based on a complex multistage probability design, which includes selection of primary sampling units (counties), household segments within the counties and finally sample persons from selected households. Data were collected through a household interview and a standardized physical examination, which was conducted in a mobile examination center. In NHANES 2001–2002, urine and serum specimens were collected from each participant, aged 6 years and older, during one of three daily scheduled examination periods (i.e., morning, afternoon and early evening). Sociodemographic information and medical histories of the survey participant and the family were collected during the household interview. NHANES 2001–2002 was conducted in 30 locations throughout the US (CDC, 2004), with a random one-third subsample consisting of 2892 NHANES study participants collectively representing the civilian, non-institutionalized US population, aged 6 years and older. Overall, the survey interview response rate was 83.9% and the exam response rate was 79.6%. Perchlorate measurements were conducted on the 2820 study participants with available urine specimen.

Demographic Variables

Sociodemographic data were self-reported by study participants. Age was grouped as children (6–11 years), adolescents (12–19 years) and adults ($\geq$20 years), consistent with the *Third National Report on Human Exposure to Environmental Chemicals* (CDC, 2005). Similarly, a race/ethnicity variable was derived from self-reported questionnaire data, resulting in four categories of race/ethnicity: non-Hispanic white, non-Hispanic black, Mexican Americans and others. Non-Hispanic blacks and Mexican Americans were over-sampled as part of NHANES; urinary perchlorate data were weighted to adjust for this oversampling (CDC, 2004). Data are not presented separately for the 'other race/ethnic groups' because of the small number of individuals in this group; however, these individuals are included in the analyses of the overall population and age and sex population groups.

Table 1. Characteristics of the population with urinary perchlorate measured, US, NHANES[a] 2001–2002.

Category	(n)	(%)
Age		
6 years and over	2820	100.0
6–11 years	374	13.3
12–19 years	828	29.4
20 years and over	1618	57.4
Sex		
Female	1485	52.7
Male	1335	47.3
Race/ethnic groups		
Non-Hispanic White	1228	43.5
Non-Hispanic Black	681	24.1
Mexican American	708	25.1
Other race/ethnic groups	203	7.2

[a]National Health and Nutrition Examination Survey.

Table 1 provides the study population characteristics by age, sex and race-ethnicity.

Laboratory Methods

During the physical examinations, spot urine specimens were collected from participants, aliquoted, and stored cold (2–4°C) or frozen until shipment. Samples collected for perchlorate measurements were shipped on dry ice to the CDC's National Center for Environmental Health. Urine samples were stored frozen (-70°C) for 3–4 years. Experiments evaluating storage at -70°C for >2 years indicate no changes in urinary perchlorate levels under these storage conditions. Urinary perchlorate was analyzed using the method of Valentin-Blasini et al. (2005). Briefly, 0.5 ml of urine was spiked with an isotopically labeled internal standard and diluted 1:1 with deionized water. This solution was subsequently analyzed using ion chromatography–electrospray ionization–tandem mass spectrometry. Perchlorate was quantified based on the peak area ratio of analyte to stable isotope-labeled internal standard. Two quality control pools were analyzed in each analytical batch with unknown samples. Reported results met the accuracy and precision specifications of the quality control/quality assurance program of the Division of Laboratory Sciences, National Center for Environmental Health, CDC (similar to rules outlined by Westgard (Westgard et al., 1981)). During analysis of urine for perchlorate, we analyzed these two quality control pools multiple times ($n = 117$) with an interday precision of 2.8% relative SD at 71 ± 2.0 μg/l and 3.0% relative SD at 4.7 ± 0.14 μg/l. In addition, reproducibility of the assay was evaluated by re-analysis of 5% of the samples, yielding an average relative percent difference of 1.5% (95% confidence interval (CI) 1.1%–2.0%). Absolute assay accuracy was verified by the blind analysis of four

different perchlorate reference solutions (AccuStandard, New Haven, CT, USA) prepared in synthetic urine (CST Technologies, Great Neck, NY, USA). We assessed perchlorate contamination by lot screening all reagents and analyzing blanks with each batch of unknowns; no contamination problems were identified.

Urinary creatinine concentrations were determined using an automated colorimetric method on a Beckman Synchron AS/ASTRA clinical analyzer (Beckman Instruments Inc., Brea, CA, USA) at the Coulston Foundation (Alamogordo, NM, USA) in 2001 and Collaborative Laboratory Services (Ottumwa, IA, USA) in 2002 (CDC, 2004). Perchlorate concentrations were adjusted using creatinine concentrations to correct for variable water excretion rates in the spot urine samples.

Estimation of Total Daily Perchlorate Dose

We estimated total daily perchlorate dose based on measured spot urine perchlorate and creatinine concentrations, and estimated daily creatinine excretion rate (g/day) computed from each individual's measured weight, height, age and sex. Specifically, daily creatinine excretion was calculated for adults based on the Cockcroft–Gault equation (Cockcroft and Gault, 1976) as modified by Mage et al. (2004), where $k = 1.93$ for males and 1.64 for females:

$$\text{Adult } g \text{ creatinine/day} = 10^{-6} * k * (140 - \text{age[yr]})$$
$$* \text{wt(kg)}^{1.5} * \text{ht(cm)}^{0.5}$$

Daily perchlorate dose was then estimated using the following formula:

$$\text{Perchlorate dose} = \mu g \text{ perchlorate/g urinary creatinine}$$
$$* g \text{ creatinine/day} * 1/\text{wt(kg)}$$

Daily perchlorate dose is not presented for children and adolescents due to the limited validation of formulas for these age groups. Also, we assumed that 100% of perchlorate intake is absorbed and excreted unmetabolized in the urine (Anbar et al., 1959; Lawrence et al., 2000). This assumption leads to underestimation of perchlorate dose in lactating women because perchlorate is secreted in human milk (Capuco et al., 2005; Kirk et al., 2005) as well as urine. Based on questionnaire data, only 26 study participants were actively lactating during the study period.

Statistical Analysis

Univariate and regression analysis of perchlorate data used survey-specific sample weights to account for differential probabilities of selection and non-response. Geometric means and percentiles of urinary perchlorate were calculated using SUDAAN PROC DESCRIPT (SUDAAN v. 9.0.0, Research Triangle Institute, Research Triangle Park, NC, USA), with CI estimated based on the method of Korn and Graubard (1998). SUDAAN PROC REGRESS was used for analysis of covariance (ANCOVA) of perchlorate levels with predictor variables of age group, sex, race/ethnicity, fasting and urinary creatinine. The ANCOVA model used to calculate the adjusted geometric means included a continuous variable for urinary creatinine and categorical variables defining age (6–11, 12–19, 20 + years), fasting (<8 h since last meal or ≥ 8 h), sex and race/ethnicity groups. Separate adjusted means are provided for sex by race/ethnicity groups because of significant interaction between these two groups. Estimates of the CI were calculated using the Taylor series linearization method (SUDAAN Users Manual, 2001).

Table 2. Geometric means and selected percentiles of urinary perchlorate concentrations (μg/l) for the US population aged 6 years and older, NHANES[a] 2001–2002.

| Category | N | GM[b] | Selected percentiles | | | | | | |
			5th	10th	25th	50th	75th	90th	95th
Total	2820	3.54 (3.29–3.81)[c]	0.78 (0.68–0.91)	1.1 (0.96–1.1)	2.0 (1.8–2.1)	3.6 (3.4–3.9)	6.2 (5.7–6.9)	10 (8.9–11)	14 (11–17)
Age: 6–11 years	374	4.93 (4.22–5.76)	1.1 (0.78–1.5)	1.6 (1.2–2.4)	3.1 (2.6–3.7)	5.2 (4.3–6.3)	8.1 (6.8–9.3)	11 (9–14)	19 (12–23)
Age: 12–19 years	828	3.80 (3.44–4.20)	0.76 (0.47–1.2)	1.1 (0.78–1.5)	2.4 (2.0–2.6)	4.4 (3.8–4.7)	6.8 (6.2–7.3)	10 (8.9–11)	12 (11–17)
Age: ≥ 20 years	1618	3.35 (3.08–3.65)	0.78 (0.69–0.87)	1.0 (0.97–1.1)	1.9 (1.7–2.0)	3.5 (3.2–3.7)	5.8 (5.2–6.5)	9.9 (8.6–11)	12 (11–16)
Males	1335	4.19 (3.93–4.46)	1.1 (0.88–1.2)	1.3 (1.2–1.6)	2.4 (2.3–2.6)	4.4 (4.2–4.5)	7.0 (6.3–7.8)	11 (9.4–12)	13 (11–17)
Females	1485	3.01 (2.74–3.31)	0.65 (0.54–0.82)	0.93 (0.82–1.0)	1.6 (1.3–1.7)	3.1 (2.7–3.4)	5.3 (4.9–5.9)	9.2 (8.2–11)	13 (11–16)
Non-Hispanic white	1228	3.51 (3.18–3.88)	0.78 (0.66–0.95)	1.0 (0.94–1.2)	1.9 (1.7–2.2)	3.6 (3.4–4.1)	6.2 (5.6–7)	10 (8.7–11)	14 (11–18)
Non-Hispanic black	681	3.51 (3.07–4.02)	0.76 (0.6–0.99)	1.1 (0.82–1.3)	2.0 (1.8–2.4)	3.6 (3.1–4.1)	5.8 (5.0–6.9)	9.1 (7.8–12)	14 (11–19)
Mexican American	708	4.02 (3.48–4.64)	1.0 (0.63–1.2)	1.4 (1.1–1.5)	2.3 (1.9–2.8)	4.4 (3.6–4.9)	7.1 (5.8–8.2)	11 (9.4–13)	14 (12–17)
Females, age 15–44	662	3.40 (3.00–3.85)	0.62 (0.37–0.83)	0.85 (0.62–1.2)	1.5 (1.2–1.9)	2.9 (2.4–3.4)	5.0 (4.0–6.4)	9.2 (7.2–12)	13 (9.1–17)

[a]National Health and Nutrition Examination Survey.
[b]Geometric mean.
[c]95% CI.

Results

We found perchlorate in all 2820 urine samples tested from NHANES 2001–2002, with levels ranging from 0.19 to 160 μg/l. Geometric means and selected percentiles of weighted perchlorate concentrations in the NHANES urine samples are shown in Table 2 (in μg/l) and Table 3 (in μg/g of creatinine). The geometric means and selected percentiles of the population are presented for the total population as well as population groups defined by age, sex and race-ethnicity.

Women of reproductive age (15–44 years) are also listed based on the recent classification of the pregnant woman/developing fetus as a potentially susceptible population (NAS, 2005). We found that women of reproductive age had urinary perchlorate levels with a median of 2.9 μg/l (CI 2.4–3.4 μg/l), 2.97 μg/g creatinine (CI 2.64–3.30 μg/g) and a 95th percentile of 13 μg/l (CI 9.1–17 μg/l), 12.1 μg/g creatinine (CI 8.15-18.1 μg/g). Of the 662 women of reproductive age, a subset (*n* = 115) were pregnant at the time of the study. The pregnant women in the study had median urinary perchlorate levels of 3.5 μg/l (CI 1.8–5.4 μg/l); 3.27 μg/g creatinine (CI 2.23–4.88 μg/g).

Children had higher median urinary perchlorate levels (5.2 μg/l; 5.79 μg/g creatinine) compared with adults (3.5 μg/l; 3.25 μg/g creatinine). We applied an ANCOVA model to further evaluate the higher levels of unadjusted urinary perchlorate observed in children compared with adolescents and adults. The adjusted geometric means for urinary perchlorate levels in each demographic group are shown in Table 4 and Figure 1. After adjustment for age, urinary creatinine, fasting, sex and race/ethnicity, urinary perchlorate levels were higher in children compared with adolescents (*P* < 0.001) or adults (*P* < 0.001). We found a significant interaction between sex and race/ethnicity and present the data for these demographic groups accordingly. Non-Hispanic white males had higher adjusted urinary perchlorate levels than non-Hispanic white females (*P* = 0.01) and non-Hispanic black males (*P* < 0.001). Fasting for 8 or more hours was associated with decreased urinary perchlorate (*P* < 0.001), likely due to a lack of dietary intake and the relatively short physiological half life of perchlorate in the human body (Anbar et al., 1959; Lawrence et al., 2000).

The geometric means and selected percentiles of estimated daily perchlorate doses for adults are shown in Table 5.

Discussion

We report the distribution of perchlorate levels in urine samples collected from a representative sample of 2820 US residents, aged 6 years and older. Based on these results, perchlorate exposure appears to be wide-spread in the US population. Human exposure to perchlorate may occur via several different routes. Perchlorate from both natural and

Table 3. Geometric means and selected percentiles of urinary perchlorate (μg/g creatinine) for the US population aged 6 years and older, NHANES[a] 2001–2002.

Category	N	GM[b]	5th	10th	25th	Selected percentiles 50th	75th	90th	95th
Total	2818	3.56 (3.34–3.80)[c]	1.10 (0.976–1.20)	1.40 (1.30–1.52)	2.17 (1.97–2.39)	3.38 (3.18–3.66)	5.61 (5.29–6.00)	9.35 (8.22–10.3)	12.7 (11.1–14.1)
Age: 6–11 years	374	5.71 (5.22–6.25)	1.91 (1.64–2.38)	2.50 (2.25–2.88)	3.64 (3.27–4.11)	5.79 (5.19–6.25)	8.33 (7.41–9.74)	13.0 (11.2–16.0)	17.4 (13.1–22.6)
Age: 12–19 years	827	2.95 (2.64–3.29)	0.922 (0.712–1.10)	1.17 (1.06–1.33)	1.88 (1.60–2.06)	2.89 (2.56–3.39)	4.48 (3.96–5.23)	7.12 (6.57–8.10)	9.87 (7.46–13.4)
Age: ≥20 years	1617	3.46 (3.20–3.73)	1.09 (0.932–1.21)	1.40 (1.27–1.54)	2.11 (1.93–2.36)	3.25 (3.04–3.59)	5.36 (4.93–5.92)	9.02 (7.61–10.2)	12.3 (10.2–14.4)
Males	1335	3.40 (3.20–3.60)	1.06 (0.891–1.16)	1.36 (1.24–1.52)	2.09 (1.94–2.27)	3.25 (3.04–3.47)	5.35 (4.93–5.86)	8.75 (7.52–9.87)	11.4 (10.1–12.7)
Females	1483	3.72 (3.39–4.09)	1.13 (1.01–1.25)	1.48 (1.30–1.60)	2.25 (1.96–2.58)	3.59 (3.20–4.10)	5.99 (5.33–6.67)	10.0 (8.15–12.1)	13.4 (11.4–16.0)
Non-Hispanic white	1227	3.76 (3.46–4.08)	1.24 (1.09–1.37)	1.54 (1.41–1.69)	2.32 (2.03–2.65)	3.54 (3.22–4.02)	5.82 (5.43–6.25)	9.42 (8.30–10.5)	12.7 (11.2–14.3)
Non-Hispanic black	680	2.53 (2.24–2.86)	0.656 (0.461–0.997)	1.00 (0.856–1.09)	1.49 (1.29–1.63)	2.54 (2.12–2.84)	4.07 (3.51–4.93)	6.87 (5.93–8.43)	10.0 (8.33–12.2)
Mexican American	708	3.77 (3.23–4.39)	1.20 (0.944–1.35)	1.52 (1.30–1.72)	2.20 (1.90–2.53)	3.51 (3.02–4.44)	6.05 (4.93–7.64)	10.4 (8.37–13.0)	14.4 (11.5–17.4)
Females, age 15–44	662	3.12 (2.72–3.57)	0.930 (0.645–1.10)	1.21 (1.05–1.39)	1.86 (1.61–2.05)	2.97 (2.64–3.30)	4.89 (3.91–6.25)	8.40 (6.32–11.7)	12.1 (8.15–18.1)

[a]National Health and Nutrition Examination Survey.
[b]Geometric mean.
[c]95% CI.

Table 4. Geometric means for urinary perchlorate (μg/l), adjusted by analysis of covariance for race/ethnicity, sex, age, fasting and urinary creatinine for ages 6 and older, NHANES 2001–2002.

Category	Adjusted geometric mean	95% confidence interval
6–11 years of age (children)	5.40[a]	(4.66–6.27)
12–19 years of age (adolescents)	3.30	(2.96–3.67)
≥20 years of age (adults)	3.41	(3.12–3.72)
Males: non-Hispanic whites	3.92[b]	(3.58–4.29)
Males: non-Hispanic blacks	2.61	(2.30–2.96)
Males: Mexican-Americans	3.94	(3.42–4.55)
Females: non-Hispanic whites	3.41[c]	(2.98–3.93)
Females: non-Hispanic blacks	3.03[d]	(2.66–3.47)
Females: Mexican-Americans	3.83	(3.12–4.70)
Fasting <8 h	3.89[e]	(3.56–4.25)
Fasting ≥8 h	3.37	(3.08–3.69)

[a]Higher than adolescents and adults ($P<0.001$).
[b]Higher than male non-Hispanic blacks ($P<0.001$).
[c]Lower than male non-Hispanic whites ($P=0.01$).
[d]Higher than male non-Hispanic blacks ($P=0.02$).
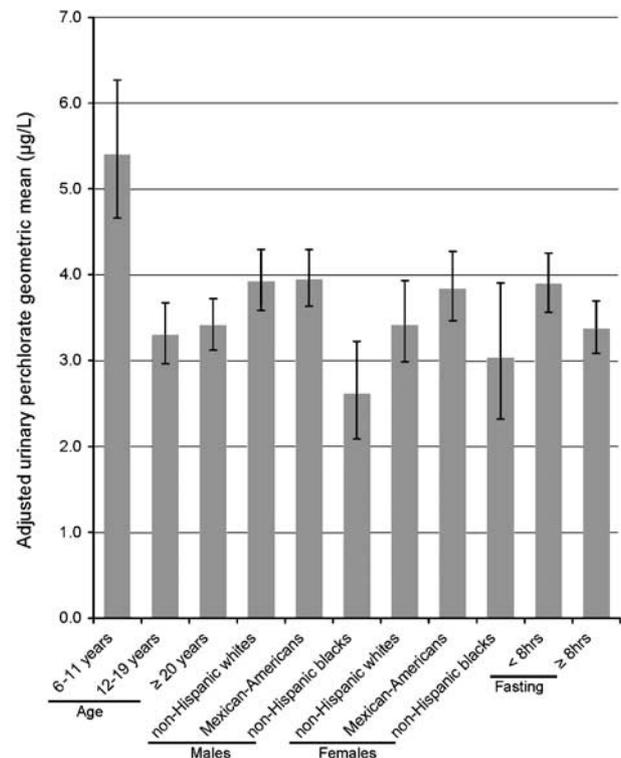[e]Higher than fasting ≥8 h ($P<0.001$).

Figure 1. Geometric means and 95th percentile confidence intervals for urinary perchlorate (μg/l), adjusted by analysis of covariance for race/ethnicity, sex, age, fasting and urinary creatinine for ages 6 and older, NHANES 2001–2002.

anthropogenic sources can contaminate drinking water and food crops. Exposure can also result from inhalation of dust containing perchlorate, especially in occupational settings (Gibbs et al., 1998). Measuring perchlorate in human urine assesses the combined exposure from all sources.

The demographic group with the highest levels of urinary perchlorate was children, similar to previously published results for urinary iodine (Caldwell et al., 2005). Covariate-adjusted urinary perchlorate levels were statistically higher in children compared with both adolescents and adults, even after adjusting for urinary creatinine (Table 4). These age-associated differences in urinary perchlorate levels could represent differences in pharmacokinetics, the relationship of dose per body weight and/or exposure. For example, dietary habits such as the consumption of milk and green leafy vegetables vary across age and ethnicity groups. Samples of dairy milk and green-leafy vegetables have been reported to contain perchlorate (Hogue, 2003; Kirk et al., 2003; FDA, 2004; Capuco et al., 2005; Jackson et al., 2005). Therefore, increased consumption of these foods could increase perchlorate exposure (Blount et al., 2006).

Several small studies have also found measurable perchlorate levels in human urine or milk. For 61 adults living in Georgia, all urine samples contained measurable levels of perchlorate, with a median of 3.2 μg/l and a log–normal distribution (Valentin-Blasini et al., 2005). Similar background levels of perchlorate (median 5.5 μg/l) were detected in urine from 13 subjects in a Southern California study (Braverman et al., 2006). Kirk et al. (2005) reported measurable levels of perchlorate in all samples of breast milk collected from 36 women residing in 18 different states (mean 10.5 μg/l).

Other previously published studies did not report measurable background levels of perchlorate, likely due to inadequate analytical sensitivity (Lawrence et al., 2000; Greer et al., 2002; Gibbs et al., 2004; Braverman et al., 2005); therefore, application of these methods resulted in reported urinary background values of less than method detection limits of 500 μg/l (Lawrence et al., 2000), 20 μg/l (Greer et al., 2002; Merrill et al., 2005) and 5 μg/l (Gibbs et al., 2004; Braverman et al., 2005). Significantly higher levels of urinary perchlorate were found in populations in northern Chile consuming tap water with perchlorate levels as high as 114 μg/l (Tellez et al., 2005). As expected, urinary perchlorate levels in these highly exposed Chilean populations (median 35 μg/l) were significantly higher than the levels found in this study.

Occupational exposure to perchlorate can lead to levels and doses that are much higher than those observed for this sample of the US population (Gibbs et al., 1998; Lamm et al., 1999; Braverman et al., 2005). Occupational survey data indicate that less than 10,000 US workers actively handle perchlorate (CDC, 1995). This small number of workers should have a minimal impact on population estimates presented here.

Measurement of a single spot urine sample was used to assess individual exposure. Urinary perchlorate levels are

Table 5. Geometric mean and selected percentiles of estimated perchlorate dose (μg/kg-day) for the US population aged 20 years and older, NHANES[a] 2001–2002.

Category	N	GM[b]	Selected percentiles		
			5th	50th	95th
Total	1532	0.066 (0.060–0.071)[c]	0.020 (0.017–0.023)	0.064 (0.059–0.069)	0.234 (0.202–0.268)
Males	726	0.071 (0.066–0.077)	0.021 (0.019–0.027)	0.069 (0.063–0.074)	0.249 (0.208–0.292)
Females	806	0.061 (0.054–0.067)	0.018 (0.015–0.022)	0.059 (0.054–0.066)	0.215 (0.184–0.260)

[a]National Health and Nutrition Examination Survey.
[b]Geometric mean.
[c]95% CI.

presented both as micrograms per liter and as micrograms per gram of urinary creatinine to allow for comparisons between different demographic groups and adjustment for differences in urinary dilution (Barr et al., 2005). For a single person, more precise exposure estimates could be derived by averaging perchlorate levels from two or three spot urine samples. However, for population estimates such as geometric means and percentiles, results of multiple persons are averaged. For these point estimates, use of a single spot urine sample from each individual would constitute one source of random error, not bias. As a source of random error, this would lead to less statistical power to detect differences in perchlorate levels between groups of interest.

Urine is the principal route by which non-lactating humans excrete perchlorate (Anbar et al., 1959; Lawrence et al., 2000). During lactation human mammary tissue expresses the sodium iodide symporter (Wolff, 1998), and thus significant transfer of perchlorate into human milk is likely. The presence of micrograms per liter concentrations of perchlorate in milk collected from US women (Kirk et al., 2005) confirms lactation as a relevant perchlorate excretion path. Additional data from another lactating mammalian species (dairy cattle) confirm that a substantial portion of a perchlorate dose can be excreted in milk (Capuco et al., 2005). If lactating women are secreting perchlorate in milk, then urine-based estimates of total perchlorate exposure for these individuals are likely to be lower than actual. However, the overall impact of lactation on our population estimates of perchlorate exposure is likely to be minimal because only 26 of the 2820 participants in our study population reported that they were currently breastfeeding a child.

Our initial measurements indicate that perchlorate exposure is widespread. The toxicological impact of perchlorate exposure at these levels is an area of ongoing research. The EPA recently set the reference dose (RfD), a dose estimated to be without appreciable risk of adverse effects during a lifetime of exposure, for perchlorate at 0.7 μg/kg-day (EPA, 2005a). This RfD was recommended by the National Academy of Sciences expert panel in their perchlorate risk assessment (NAS, 2005). To compare our measured per-

chlorate concentrations in spot urine samples with this toxicological benchmark dose, we estimated daily dose based on physiological parameters and measured spot urine perchlorate and creatinine. Estimation of perchlorate dose in adults revealed a median of 0.066 μg/kg-day and a 95th percentile of 0.234 μg/kg-day. These estimated perchlorate dose levels are lower than the current EPA reference dose of 0.7 μg/kg-day. Only 11 adults had estimated perchlorate exposure in excess of the reference dose.

The NAS has specified pregnant women, fetuses and infants as populations who may be more sensitive to the potential health effects of perchlorate exposure (NAS, 2005). Mild hypothyroidism during pregnancy can be associated with subsequent cognitive deficits in children (Haddow et al., 1999; Klein et al., 2001). Additionally, active expression of the sodium iodide symporter in the placenta and lactating breast tissue allows perchlorate exposure of the mother to be distributed to the developing fetus and infant. Perchlorate measurement began at 6 years of age in our study, so we do not have exposure information for infants. Women of reproductive age can be used as a surrogate population for assessing fetal exposure. Women of reproductive age had a median estimated perchlorate dose of 0.057 μg/kg-day and a 95th percentile of 0.214 μg/kg-day. Daily perchlorate exposure doses were also estimated for the pregnant women in the study who had complete data sets for age, height and weight ($N = 110$). This population of pregnant women had an estimated median perchlorate dose of 0.066 μg/kg-day. These estimated perchlorate dose levels are lower than the current EPA reference dose of 0.7 μg/kg-day.

Conclusions

We assessed urinary perchlorate levels in a US reference population and present the data here stratified by age, sex and race/ethnicity. We found perchlorate in all human urine samples tested, indicating widespread trace-level perchlorate exposure in the general population. We estimated daily perchlorate dose and found that the 95th percentile of

estimated dose is less than the EPA RfD. The results provide information for risk modeling and provide a reference range for comparisons with results from other potentially exposed population groups. These data provide the first population-based assessment of the magnitude and prevalence of perchlorate exposure in the US.

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