



Testimony
Committee on Energy and Commerce
Subcommittee on Environment and
Hazardous Materials
United States House of Representatives

**CDC's Perchlorate Biomonitoring Activities
and Study Results**

Statement of

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Good morning Mr. Chairman and Members of the Subcommittee:

My name is Dr. James Pirkle, Deputy Director for Science in the Division of Laboratory Sciences of the National Center for Environmental Health at the Centers for Disease Control and Prevention (CDC).

I am pleased to appear here today before the Subcommittee to discuss results of two studies conducted by CDC researchers investigating exposure to perchlorate in the U.S. population and the relationship between exposure to perchlorate and thyroid hormone levels.

In my presentation, I will first provide a brief background on CDC's National Biomonitoring Program and efforts to measure perchlorate, then discuss results of our study examining perchlorate exposure in the U.S. population, and finally, discuss findings from our study that focused on the relationship between exposure to perchlorate and hormone levels.

Briefly, perchlorate is a chemical compound used in solid rocket propellant, explosives, pyrotechnics, flares, and a few other products. It also can form naturally in the atmosphere, producing trace levels in precipitation. Perchlorate in irrigation water can contaminate crops. High doses of perchlorate are known to reduce the amount of thyroid hormone produced; in the past, perchlorate was one medical treatment used to reduce the excessive amount of thyroid hormone produced in people with hyperthyroidism. Therapeutic doses of perchlorate used

in the 1950s and 1960s to treat hyperthyroidism were much higher than levels that people are exposed to in the environment.

The Division of Laboratory Sciences at CDC's National Center for Environmental Health conducts the National Biomonitoring Program, which measures environmental chemicals, such as perchlorate, in blood and/or urine to assess the exposure of the U.S. population and exposure of selected population groups. Our laboratory has been conducting work in biomonitoring for 32 years and currently can measure more than 400 chemicals in human blood or urine. Biomonitoring measurements are reported in the scientific literature and, since 2001, in CDC's *National Report on Human Exposure to Environmental Chemicals*. As part of this National Biomonitoring Program, CDC researchers developed a method to measure perchlorate in urine and published that method in the peer-reviewed literature in 2005. This method has an excellent ability to measure perchlorate even at low levels and to distinguish perchlorate from other chemicals.

Using this new method, our laboratory measured perchlorate in the urine of participants in CDC's National Health and Nutrition Examination Survey (NHANES) for the years 2001-2002. The NHANES survey is designed to provide a unique assessment of the health and nutritional status of the civilian non-institutionalized U.S. population. The survey has been conducted multiple times since the early 1970s. For the survey years 2001-2002, NHANES also measured serum levels of two thyroid hormones in survey participants. These

hormones are total thyroxine, also called total T4, and thyroid stimulating hormone, commonly referred to as TSH. In the future, NHANES will evaluate additional measures of thyroid function.

From their analysis of the results, CDC researchers published two papers, the first describing levels of urinary perchlorate in people aged 6 years and older, and the second examining the relationship between levels of urinary perchlorate and thyroid hormone levels in people aged 12 years and older.

In the first paper, which described perchlorate exposure in people aged 6 years and older in the U.S. population, the researchers found measurable levels of perchlorate in the urine of all 2820 survey participants, indicating widespread human exposure to this chemical in the United States. The researchers also found that levels of perchlorate in children were higher than levels found in adolescents and adults, and this difference was statistically significant.

The researchers compared the levels found in the population with the Environmental Protection Agency (EPA) reference dose. The EPA reference dose is defined as an estimate of a daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime. The EPA reference dose for perchlorate is 0.7 micrograms per kilogram of body weight per day. The National Academy of Sciences recommended this reference dose in 2005. For adults, equations to estimate dose from urine perchlorate concentrations are available. We calculated dose estimates for each adult in the

2001-2002 survey on the basis of each person's urine perchlorate level and found that only 11 adults (out of 1532 people) had levels exceeding this reference dose (RfD). The median estimated total daily perchlorate dose for adults was about one-tenth of the RfD, and the 95th percentile was about one-third of the RfD.

The second study examined the relationship between urine perchlorate levels and thyroid hormone levels – specifically total thyroxine and TSH. Thyroxine and TSH measurements were available for people aged 12 years and older.

Thyroxine regulates the body's metabolism and is important for proper development of the brain. TSH is secreted by the pituitary gland and regulates the production of thyroxine by the thyroid gland. When the thyroid is not producing adequate amounts of thyroxine, TSH levels increase in order to stimulate more production. At high doses, perchlorate is known to block iodine uptake into the thyroid, causing decreased production of thyroxine and increased production of TSH. This second study examined perchlorate levels of the U.S. population, levels that are much lower than those previously known to decrease thyroxine and increase TSH.

Among men, the researchers found no relationship between perchlorate levels and levels of the thyroid hormones thyroxine and TSH. After the initial analyses of the results obtained for women, the researchers divided women for further analysis into two groups: those with urinary iodine levels above and below a cut-off of 100 micrograms per liter. This cut-off is based on a World Health

Organization finding that the frequency of goiter from hypothyroidism increases in populations that have a median urinary iodine level of less than 100 micrograms per liter. It is reasonable to hypothesize that people with lower urinary iodine levels could be more vulnerable to a perchlorate effect on thyroid function.

The researchers found that, among women who had urinary iodine levels that were less than 100 micrograms per liter, perchlorate levels were associated with both thyroxine and TSH levels. For both thyroxine and TSH, these associations were statistically significant and consistent in direction with those expected from perchlorate inhibition of iodine uptake into the thyroid. That is, higher perchlorate levels were associated with lower levels of thyroxine and higher levels of TSH. However, thyroid hormone levels remained within clinically normal ranges. Thirty-six percent of women in the U.S. population have urinary iodine levels less than 100 micrograms per liter, a percentage that corresponds to about 43 million women.

Among women with urinary iodine levels greater than or equal to 100 micrograms per liter, the researchers found that perchlorate levels showed a statistically significant association with TSH but not with thyroxine. Change in TSH levels is a more sensitive indicator of decreased thyroid function, which may account for this finding in this group of women.

This was the first study to examine the association of perchlorate with thyroid hormone levels in women who had levels of urinary iodine that were less than 100 micrograms per liter. The differences we saw in study findings between men and women merit further research. Other research has shown that women have higher rates of hypothyroidism than men.

The finding of an association between perchlorate exposure and thyroid function in these women was unexpected based on previous research and has prompted further study. CDC researchers are planning a second study to affirm their findings and evaluate additional measures of thyroid function.

Adequate intake of iodine has previously been recognized as important for healthy thyroid function. Our study results would reinforce that recommendation for women.

In summary, these two studies show that low perchlorate exposure is widespread in the U.S. population but generally is below the EPA RfD in our study population of women aged 20 years and older. Among men, perchlorate levels were not associated with hormone levels. Among women with lower levels of iodine in their urine, perchlorate exposure that is common in the U.S. population was associated with small- to-medium-size changes in thyroid hormone levels.

Adequate intake of iodine substantially diminishes the association of perchlorate exposure with thyroid hormone levels in women.

Copies of both studies have been provided to the Committee. The publication “Urinary Perchlorate and Thyroid Hormone Levels in Adolescents and Adult Men and Women Living in the United States” is available on line at:

<http://www.ehponline.org/members/2006/9466/9466.pdf>

Mr. Chairman, this concludes my prepared statement. Thank you for giving me the opportunity to speak before the Subcommittee. I would be happy to respond to any questions that you or other Members of the Subcommittee may have.

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 ($>0.05 \mu\text{g/l}$) 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 $3.6 \mu\text{g/l}$ ($3.38 \mu\text{g/g}$ creatinine) and a 95th percentile of $14 \mu\text{g/l}$ ($12.7 \mu\text{g/g}$ 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 $0.234 \mu\text{g/kg-day}$ [CI $0.202\text{--}0.268 \mu\text{g/kg-day}$] and is below the EPA reference dose ($0.7 \mu\text{g/kg-day}$), 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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Keywords: perchlorate, human, urine, exposure assessment, biomonitoring, NHANES.

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 $4 \mu\text{g/l}$ to a

maximum at $420 \mu\text{g/l}$ (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 (Wynngaarden 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 ~ 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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selective analytical method capable of quantifying perchlorate in human urine as low as $0.05 \mu\text{g/l}$ (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 (≥ 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)	(%)
<i>Age</i>		
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
<i>Sex</i>		
Female	1485	52.7
Male	1335	47.3
<i>Race/ethnic groups</i>		
Non-Hispanic White	1228	43.5
Non-Hispanic Black	681	24.1
Mexican American	708	25.1
Other race/ethnic groups	203	7.2

^aNational 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 ($2\text{--}4^\circ\text{C}$) 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 $71 \pm 2.0 \mu\text{g/l}$ and 3.0% relative SD at $4.7 \pm 0.14 \mu\text{g/l}$. 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:

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

Daily perchlorate dose was then estimated using the following formula:

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

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 ($\mu\text{g/l}$) 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)

^aNational Health and Nutrition Examination Survey.

^bGeometric mean.

^c95% CI.

Results

We found perchlorate in all 2820 urine samples tested from NHANES 2001–2002, with levels ranging from 0.19 to 160 $\mu\text{g/l}$. Geometric means and selected percentiles of weighted perchlorate concentrations in the NHANES urine samples are shown in Table 2 (in $\mu\text{g/l}$) and Table 3 (in $\mu\text{g/g}$ 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 $\mu\text{g/l}$ (CI 2.4–3.4 $\mu\text{g/l}$), 2.97 $\mu\text{g/g}$ creatinine (CI 2.64–3.30 $\mu\text{g/g}$) and a 95th percentile of 13 $\mu\text{g/l}$ (CI 9.1–17 $\mu\text{g/l}$), 12.1 $\mu\text{g/g}$ creatinine (CI 8.15–18.1 $\mu\text{g/g}$). 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 $\mu\text{g/l}$ (CI 1.8–5.4 $\mu\text{g/l}$); 3.27 $\mu\text{g/g}$ creatinine (CI 2.23–4.88 $\mu\text{g/g}$).

Children had higher median urinary perchlorate levels (5.2 $\mu\text{g/l}$; 5.79 $\mu\text{g/g}$ creatinine) compared with adults (3.5 $\mu\text{g/l}$; 3.25 $\mu\text{g/g}$ 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 ($\mu\text{g/g}$ creatinine) 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	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)

^aNational Health and Nutrition Examination Survey.

^bGeometric mean.

^c95% CI.

Table 4. Geometric means for urinary perchlorate ($\mu\text{g/l}$), 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)

^aHigher than adolescents and adults ($P < 0.001$).

^bHigher than male non-Hispanic blacks ($P < 0.001$).

^cLower than male non-Hispanic whites ($P = 0.01$).

^dHigher than male non-Hispanic blacks ($P = 0.02$).

^eHigher than fasting ≥ 8 h ($P < 0.001$).

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 $3.2 \mu\text{g/l}$ and a log-normal distribution (Valentin-Blasini et al., 2005). Similar background levels of perchlorate (median $5.5 \mu\text{g/l}$) 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 $10.5 \mu\text{g/l}$).

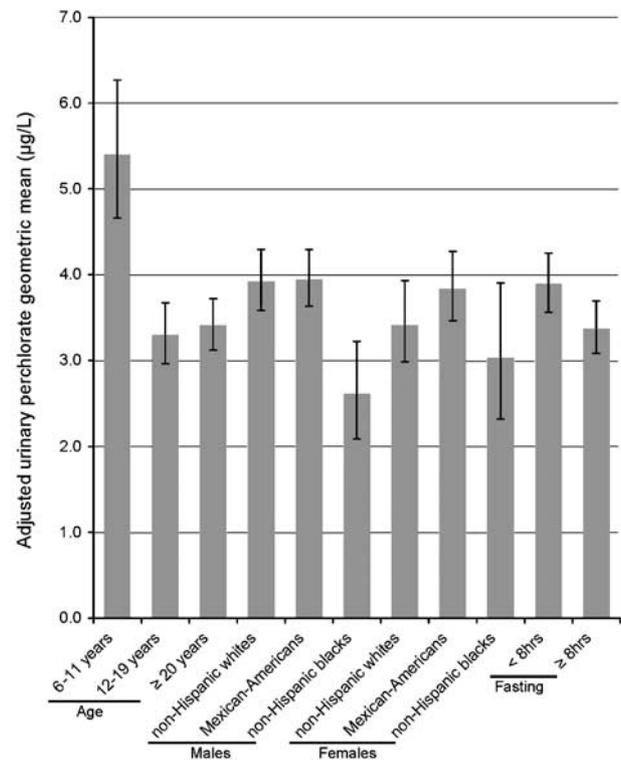


Figure 1. Geometric means and 95th percentile confidence intervals for urinary perchlorate ($\mu\text{g/l}$), adjusted by analysis of covariance for race/ethnicity, sex, age, fasting and urinary creatinine for ages 6 and older, NHANES 2001–2002.

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 $500 \mu\text{g/l}$ (Lawrence et al., 2000), $20 \mu\text{g/l}$ (Greer et al., 2002; Merrill et al., 2005) and $5 \mu\text{g/l}$ (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 $114 \mu\text{g/l}$ (Tellez et al., 2005). As expected, urinary perchlorate levels in these highly exposed Chilean populations (median $35 \mu\text{g/l}$) 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 ($\mu\text{g}/\text{kg}\text{-day}$) 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)

^aNational Health and Nutrition Examination Survey.^bGeometric mean.^c95% 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 $0.7 \mu\text{g}/\text{kg}\text{-day}$ (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 $0.066 \mu\text{g}/\text{kg}\text{-day}$ and a 95th percentile of $0.234 \mu\text{g}/\text{kg}\text{-day}$. These estimated perchlorate dose levels are lower than the current EPA reference dose of $0.7 \mu\text{g}/\text{kg}\text{-day}$. 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 $0.057 \mu\text{g}/\text{kg}\text{-day}$ and a 95th percentile of $0.214 \mu\text{g}/\text{kg}\text{-day}$. 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 $0.066 \mu\text{g}/\text{kg}\text{-day}$. These estimated perchlorate dose levels are lower than the current EPA reference dose of $0.7 \mu\text{g}/\text{kg}\text{-day}$.

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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