Title
Maternal perchlorate exposure in pregnancy and altered birth outcomes

Authors
Rubin, Rainbow
Pearl, Michelle
Kharrazi, Martin
et al.

Publication Date
2017-10-01

DOI
10.1016/j.envres.2017.05.030

Peer reviewed

HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Environ Res. 2017 October ; 158: 72–81. doi:10.1016/j.envres.2017.05.030.

Maternal perchlorate exposure in pregnancy and altered birth outcomes☆

Rainbow Rubin[1], **Michelle Pearl**[2], **Martin Kharrazi**[3], **Benjamin C. Blount**[4], **Mark D. Miller**[5], **Elizabeth N. Pearce**[6], **Liza Valentin-Blasini**[4], **Gerald DeLorenze**[7], **Jane Liaw**[1], **Andrew N. Hoofnagle**[8], and **Craig Steinmaus**[1,9]

[1]School of Public Health, University of California, Berkeley, CA

[2]Sequoia Foundation, La Jolla, CA

[3]Environmental Health Investigations Branch, California Department of Public Health, Richmond, CA

[4]Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA

[5]Pediatric Environmental Health Specialty Unit, University of California, San Francisco, CA

[6]Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Boston, MA

[7]Division of Research, Kaiser Permanente Northern California, Oakland, CA

[8]Departments of Lab Medicine and Medicine, University of Washington, Seattle, Washington, USA

[9]Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA

Abstract

Background—At high medicinal doses perchlorate is known to decrease the production of thyroid hormone, a critical factor for fetal development. In a large and uniquely exposed cohort of pregnant women, we recently identified associations between environmental perchlorate exposures and decreased maternal thyroid hormone during pregnancy. Here, we investigate whether perchlorate might be associated with birthweight or preterm birth in the offspring of these women.

☆The views expressed are those of the authors and do not necessarily represent those of the Centers for Disease Control and Prevention, the Office of Environmental Health Hazard Assessment, the California Environmental Protection Agency, the California Department of Public Health, or the State of California.

*Corresponding author: Craig Steinmaus, University of California, Berkeley, School of Public Health, Department of Environmental Health Sciences, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, CA. Tel.: (510) 990-8354, craigs@berkeley.edu.

The authors declare they have no competing financial interests.

Methods—Maternal urinary perchlorate, serum thyroid hormone concentrations, birthweight, gestational age, and urinary nitrate, thiocyanate, and iodide were collected in 1,957 mother-infant pairs from San Diego County during 2000–2003, a period when the county's water supply was contaminated with perchlorate. Associations between perchlorate exposure and birth outcomes were examined using linear and logistic regression analyses adjusted for maternal age, weight, race/ethnicity, and other factors.

Results—Perchlorate was not associated with birth outcomes in the overall population. However, in analyses confined to male infants, $\log_{10}$ maternal perchlorate concentrations were associated with increasing birthweight (β=143.1 gm, p=0.01), especially among preterm births (β=829.1 g, p<0.001). Perchlorate was associated with male preterm births >2500 g (odds ratio=3.03, 95% confidence interval=1.09–8.40, p-trend=0.03). Similar associations were not seen in females.

Conclusions—This is the first study to identify associations between perchlorate and increasing birthweight. Further research is needed to explore the differences we identified related to infant sex, preterm birth, and other factors. Given that perchlorate exposure is ubiquitous, and that long-term impacts can follow altered birth outcomes, future research on perchlorate could have widespread public health importance.

Keywords

perchlorate; thyroid; birthweight; pregnancy; preterm

INTRODUCTION

Perchlorate (ClO_4^-) is a highly stable oxidizing chemical component of missile fuel, road flares, and other products. Perchlorate exposure in the US is ubiquitous, typically occurring through contaminated food or water. In a recent nationwide US survey, perchlorate was detected in the urine of every person tested (1).

At medicinal levels (e.g. 800 mg), perchlorate competitively inhibits uptake of iodide by the sodium iodide symporter (NIS) in the thyroid gland (2). Iodide is the predominant form of iodine found in diet. Iodide anion accounts of >90% of total iodine in urine and is the biologically available form that is transported into the thyroid to produce thyroid hormones. Since iodide is a key component of thyroid hormone, inhibiting its uptake into the thyroid can decrease thyroid hormone production. In the developing fetus and child, thyroid hormone is vital for proper development, and decreases in this hormone have been linked to significant decreases in IQ and other adverse neurologic outcomes (3–6). Pregnancy is a time of thyroid stress and increased iodine demands, and this could lead to pregnancy being a period of particular susceptibility to perchlorate (7).

Thyroxine (T4) is the major circulating form of thyroid hormone, and free thyroxine (fT4) is its non-protein bound form. Thyroid stimulating hormone (TSH) is produced by the pituitary in response to low thyroid hormone concentrations in plasma, and stimulates the thyroid to produce more T4. Elevated TSH acts as a sensitive marker for thyroid stress since TSH is commonly effective at maintaining adequate serum concentrations of T4. In the largest study to date of perchlorate in pregnant women, we identified statistically significant associations

between increasing urinary perchlorate concentrations and decreasing serum T4 and fT4 and increasing TSH concentrations (8). This study involved samples and data collected from pregnant women who gave birth in San Diego County between November 2000 and March 2003. This was a time when a large groundwater plume of perchlorate from a former perchlorate manufacturing plant contaminated the Las Vegas Wash, a tributary of the Colorado River (9). This contamination led to widespread perchlorate exposure, since the Colorado River supplies drinking water for 15–20 million people in Nevada, Arizona, and California, including much of San Diego County. The contamination resulted in perchlorate concentrations approaching the current California regulatory standard of 6 μg/L in the county's major drinking water supply. Other water sources in the county had much lower perchlorate concentrations. This exposure situation, combined with likely variations in intake of perchlorate from food, provided a wide range of perchlorate exposure among county residents.

Although several studies, including ours, have linked perchlorate to impacts on thyroid function, few studies have examined perchlorate in relation to overt adverse health effects. Based on the associations we identified in our previous study, and the well-known role thyroid hormone plays in fetal development, we investigated whether maternal perchlorate may have impacted birthweight or gestational age in our San Diego cohort. We also evaluated whether any associations we identified might be greater in certain potentially susceptible subpopulations. In previous research, perchlorate-thyroid hormone associations were greatest in subjects with elevated intakes of thiocyanate and nitrate, or with very high or low urinary levels of iodide (1, 8, 10). Thiocyanate (from foods or tobacco smoke) and nitrate (from foods or contaminated water) also competitively inhibit thyroid iodide uptake, and may have additive impacts with perchlorate (2). Previous research has also shown that birth outcomes or the adverse effects of environmental chemicals may be related to gender, ethnicity or race, or migration status (11, 12), and we assessed potential susceptibility related to these factors as well.

METHODS

Study design and data collection

Subjects were a convenience sample of pregnant women and their newborns from San Diego County, delivered from November 2000 to March 2003, and already recruited as part of Project Baby's Breath (PBB), a study of tobacco and other environmental exposures during pregnancy. PBB involved 14 hospitals and 41 community clinics and obstetrical care providers widely spread throughout the county, and the collection and frozen storage of urine, blood, and cord blood samples originally obtained for non-study purposes. Urine samples assayed for the present analysis were left over from spot urine samples collected from PBB subjects for pregnancy tests at a median of seven weeks gestation. After pregnancy testing, clinic staff transferred the remaining urine into 5ml Corning cryovials that were refrigerated and transferred within one day to a central laboratory for storage at −20°C. Perchlorate is stable for many months in water at room temperature (13), and for years in frozen urine (14). Serum samples assayed for the present analysis were left over from samples collected by obstetrical care providers at approximately 15–20 weeks

gestation from PBB subjects who participated in the California Prenatal Screening (PNS) Program (15). After collection in 4ml serum separator tubes, specimens were spun down and tested for chromosomal abnormalities and neural tube defects, with a median time between collection and PNS testing of three days. After PNS testing and 1–2 days of refrigeration, remaining serum from PBB study participants was transferred to 4ml Corning cryovials and stored at −20°C. Samples not assayed within seven days of collection were excluded from the PNS and not available for PBB. Mannisto *et al.* reported that fT4 or TSH were relatively stable for 6 days at 4°C and up to 23 years at −25°C (16). Information on mother's age, highest education, prenatal weight, payment method (e.g., private insurance vs. MediCal), and race/ethnicity was collected from birth records. Information on prenatal weight was derived from the PNS program. Gestational age was calculated using the date of conception estimated from ultrasound and information on last menstrual period collected during prenatal screening, a method that produces more accurate gestational age estimates than relying on last menstrual period dates from birth records (17, 18). For subjects not participating in prenatal screening (approximately 10%), gestational age was based on the date of last menstrual period recorded on birth records. Urine and serum samples, PNS program data, and birth records were linked using probabilistic matching software. PNS to birth match rates using this method are generally 93% (19). Informed consent was obtained for collection of leftover urine and blood specimens for the PBB study and for future testing of stored specimens for environmental contaminants. PNS program participants signed a consent/refusal form and received a privacy notification regarding research use of their specimen. The PBB study and the study presented here were approved by the State of California Committee for the Protection of Human Subjects.

Laboratory measurements

Urinary perchlorate is the most common biomarker for evaluating perchlorate exposure, since most ingested perchlorate is excreted unchanged in the urine (20). Urine samples were shipped overnight to the Centers for Disease Control and Prevention (CDC) on dry ice and analyzed by the CDC's Perchlorate Biomonitoring Laboratory for perchlorate (detection limit, 0.05 μg/L), thiocyanate (20 μg/L), nitrate (700 μg/L), and iodide (0.5 μg/L) using ion chromatography tandem mass spectrometry (21). Urinary cotinine levels were measured in 856 subjects by the CDC as part of a previous study. Results met the division's quality control criteria for accuracy and precision similar to those outlined in Caudill *et al.* (22). After overnight shipping on dry ice, serum samples were measured for total T_4, free thyroxine (fT_4), thyroid stimulating hormone (TSH)), and thyroperoxidase (TPO) and thyroglobulin (Tg) antibody concentrations at the University of Washington, Seattle, using a Beckman automated immunoassay chemiluminescence platform and microparticle enzyme immunoassay (Beckman Coulter). Quality control measures included 2-level quantitative controls for each assay on every reagent run, monitoring run integrity using Levey-Jennings charts, and participation in proficiency surveys by the College of American Pathologists. Manufacturers' values for TPO and Tg antibody positivity are >9 and >4 IU/mL, respectively.

Statistical analysis

This study initially included all pregnant women (n=2,184) who participated in PBB and had a urine and/or blood sample with sufficient remaining specimen for laboratory analyses. Additional exclusion criteria for the analyses presented here included missing data on urinary perchlorate, thiocyanate, nitrate, iodide, or creatinine concentrations (n=139); missing data on birthweight or gestational age (n=32); multiple births (e.g. twins)(n=19); birth or pregnancy complications (e.g., hypertension, breech birth, diabetes)(n=30); or abnormally high maternal T4 (>20 μg/dL) or TSH (>10 μIU/mL) values (n=7).

Most statistical analyses were done using SAS version 9.1 (SAS Institute Inc.) and all reported p-values are two-sided. Univariate analyses of urinary analytes, serum thyroid hormones, birth outcomes, and sociodemographic variables were examined for distributions and outliers. Unadjusted analyses of perchlorate concentrations and birth outcomes by various sociodemographic characteristics were conducted using Wilcoxon rank sum tests, Spearman correlation coefficients, and Chi-square tests. Mean concentrations of perchlorate and the other urinary analytes in this study were compared to those calculated for reproductive-aged women (ages 15–45 years) from the 2001–2002 National Health and Nutrition Examination Survey using methods described elsewhere (10).

Associations between perchlorate and birthweight were examined using linear regression analyses in models both unadjusted and adjusted for urinary creatinine ($\log_{10}$), maternal age (year), maternal weight (lbs), race (indicator variables for White, Black, Asian, Other), infant sex, maternal education (<high school, some high school, high school, beyond high school), Caesarean birth, medical insurance (private vs. MediCal), timing of urine sample collection (weeks gestation), ethnicity (Hispanic vs. non-Hispanic), and mother's birthplace (Mexico vs. US vs. other). When assessing subgroups based on race and ethnicity, we classified Hispanics as all subjects identifying as Hispanic regardless of race, and our other categories of race excluded Hispanics. Independent variables, including perchlorate, thiocyanate, nitrate, iodide, and creatinine were $\log_{10}$ transformed to stabilize variance and reduce outlier influence. Variables that changed regression coefficients by more than 10% were retained in the final models and included creatinine, maternal age and weight, race, and sex. In addition to linear regression analyses, perchlorate-birthweight associations were evaluated by calculating mean birthweights by quartiles of perchlorate concentrations using proc GLM. Potential effect modification by factors such as infant sex, co-exposure to other NIS-related agents (nitrate, iodide, thiocyanate), and other factors (e.g. Cesarean birth, cotinine) was assessed by stratifying the linear regression analyses based on these factors or by entering interaction terms (e.g. perchlorate*thiocyanate) into the regression models. For nitrate, thiocyanate, and cotinine category cutoff points were based on tertiles. For urinary iodide we used categories of <100, 100–300, and >300 μg/L which correspond to median values used by the World Health Organization (WHO) to define iodine deficiency, normal values, and elevated iodine levels, respectively, in non-pregnant populations ≥6 years old (23). A lower category cutoff of 150 μg/L, the WHO recommended population level for pregnant women, was assessed but produced similar results. Because previous studies have reported differences in birth outcomes by ethnicity or mother's migration status, stratified analyses were also done based on these factors (24).

Because the known toxic mechanism of perchlorate involves thyroid hormone and altered thyroid hormone levels have been linked to adverse birth outcomes (25), mediation by this pathway was assessed by comparing perchlorate-birthweight linear regression coefficients with and without adjustment for T4, fT4, or $\log_{10}$ TSH levels and using the Sobel test and the SAS mediation macro provided by Valeri and VanderWeele (26).

Logistic regression was used to calculate odds ratios for preterm birth (<37 weeks gestation) across quartiles of urinary perchlorate concentration using the lower quartile as the reference. These models also included $\log_{10}$ creatinine, maternal age and weight, race, and infant sex. The impact of adjusting for other factors such as iodide, Cesarean birth, mother's education, or sample collection timing was also assessed. Because the health implications of preterm birth can vary by birthweight (27), and to explore possible impacts of perchlorate on birthweight and gestational age combined, we also calculated ORs for various birthweight-gestational age strata (preterm birth below 2500 g, term birth below 2500 g, preterm birth 2500 grams or above, and term birth 2500 grams or above) using the categories similar to those proposed by Yerushalmy (27). Here, all births not in the selected category were used as the reference group. The adjusted proportions of births in each category were assessed using the adjprop command in StataSE 14.0.

RESULTS

Characteristics of the study population

Overall, 1,957 mother-infant pairs met the inclusion criteria for this study. Distributions of perchlorate, thyroid hormones and other factors in the study population as a whole are shown in Table 1. Urine perchlorate concentrations ranged from 0.23 to 177 μg/L, with a mean of 8.57 μg/L, which is higher than that seen in reproductive-aged US women from the 2001–2002 US National Health and Nutrition Examination Survey (mean of 4.73 μg/L) (Table A1). The median urinary iodide concentration was 153 μg/L, which is similar to the recommended population level for pregnant women of 150 μg/L (23).

The numbers of subjects, as well as mean perchlorate concentrations and birthweights, and the proportions of preterm births, in categories of various sociodemographic characteristics are shown in Table 2. Overall, the study population was mostly Hispanic (69.1%), mostly used public medical insurance (69.9%), and mothers were mostly born in the US (45.1%) or Mexico (47.7%). Sociodemographic characteristics were similar in included and excluded subjects (Table A2). Mean perchlorate concentrations were higher in Blacks than Hispanics (11.85 vs. 8.42 μg/L, $p<0.001$), and lower in mothers born in Mexico and elsewhere compared to those born in the US (means of 8.40 ($p=0.02$), 7.63 ($p=0.02$), and 8.90 μg/L, respectively). Lower birthweights were associated with female sex (3341.4 vs. 3498.2 g, $p<0.001$), decreasing maternal age (Spearman $R=0.08$, <0.001), decreasing maternal weight (Spearman $R=0.26$, $p<0.001$), and normal vaginal delivery (3400.8 vs. 3480.5 g, $p<0.001$). Preterm births were somewhat higher in those with increasing maternal age (p-trend=0.06), and somewhat lower in mothers born in Mexico than in the US (7.5 vs. 8.8%, OR=0.84, 95% CI: 0.60–1.17).

Perchlorate-birthweight

In linear regression analyses, clear associations between $\log_{10}$ perchlorate and birthweight were not seen when both sexes were combined (Table 3). However, in analyses stratified by sex, an association was seen for male births (β=143.1 gram increase for each 10-fold increase in perchlorate, p=0.01), but not for female births (β=−38.3 grams, p=0.49). Given a median birthweight of 3498 grams in male infants, the regression coefficient of 143.1 grams identified here represents a 4.1 percent increase in birthweight for each 10-fold increase in urinary perchlorate concentration. In male infants, perchlorate-birthweight associations were greater in preterm births (β=829.1, p<0.001) than in births ≥37 weeks gestation (β=97.3, p=0.06). Associations in male infants were also greater for those with US born mothers (β=297.2, p<0.001) (Figure 1) than those with Mexico-born mothers (β=29.9, p=0.68). In male births of US born mothers similar results were seen in categorical analyses where mean birthweights increased from the lowest to highest perchlorate quartile (3402.5, 3461.6, 3563.6, 3566.8 grams, respectively; p-trend=0.009) (Table A3). In US born mothers, results were similar in strata of Hispanics and Whites (data not shown). Adjusting for thiocyanate, iodide, nitrate, cotinine, education, Caesarean birth, Tg or TPO positivity, race, or insurance type had little impact on these birthweight results.

Analyses using interaction terms or stratified analyses showed no clear evidence of interaction with thiocyanate or nitrate on perchlorate-birthweight associations in either sex (not shown). The perchlorate-birthweight association was greater for male births with maternal iodide concentrations below 100 μg/L (β=177.3, p=0.05) and above 300 μg/L (β=301.1, p=0.06) compared to those with iodide concentrations between these levels (β=25.4, p=0.76) (Table 3).

Perchlorate-preterm birth

In both sexes combined, and in males and females separately, clear associations were not seen between increasing perchlorate quartiles and ORs for all preterm births combined (Table 4). However, the OR for having a preterm birth ≥2500 grams comparing the upper to lower perchlorate quartiles was elevated in male (OR=3.03; 95% CI: 1.09–8.40; p-trend=0.03) but not female infants (OR=1.07; 95% CI: 0.39–2.89). For male infants, this OR was greater in infants of Mexico (OR=4.33; 95% CI: 1.05–17.87) vs. US born mothers (OR=1.46; 95% CI: 0.33–6.55) (Figure A1). Adjustments for thiocyanate, nitrate, iodide, cotinine, maternal weight or education, Tg or TPO positivity, or public vs. private insurance use, and removing the 191 subjects for whom gestational age was estimated based solely on birth certificate data, had little impact on perchlorate-preterm ORs.

For preterm births <2500 grams, the OR in male infants comparing the upper to lower perchlorate quartiles was below 1.0 (OR=0.12, 95% CI: 0.02–0.61) although the number of births in this category was small (n=2 cases in the upper perchlorate quartile). This OR was close to 1.0 in females infants (OR=1.06; 95% CI: 0.28–3.97). Analyses stratified by mother's birthplace suggest the low OR in male infants for preterm birth <2500 grams primarily occurs in infants of US born mothers although sample sizes were very small (e.g. a total of 3 preterm births <2500g in the upper three perchlorate quartiles) (Figure A1).

Figure 2 displays the unadjusted proportions of all male births in several additional birthweight-gestational age categories, comparing subjects in the upper and lower perchlorate quartiles. As shown, there was a greater percentage of births in the preterm 2500–4000 g (9.9 vs. 3.8%) group and a lower percentage in the preterm <2500 g (5.0% vs. 0.8%) group among subjects in the higher vs. lower perchlorate quartiles. Only small perchlorate-related differences were seen in the other birthweight-gestational age categories, including term >4000 g babies. Adjustments for creatinine, maternal age and weight, and race had little impact on these results but led to non-robust results in categories with small numbers (not shown).

Thyroid hormone mediation

For the analyses of possible mediation of the perchlorate-birthweight association by thyroid hormone, 862 male births had data on maternal serum T4, fT4, and TSH concentrations. In these subjects, increasing $\log_{10}$ perchlorate was associated with decreasing T4 ($\beta=-0.73$, $p<0.001$) (Table A4), decreasing fT4 ($\beta=-0.043$, $p=0.05$), and increasing $\log_{10}$ TSH ($\beta=0.069$, $p=0.03$). Serum T4 was inversely associated with birthweight, when adjusting for $\log_{10}$ perchlorate ($\beta=-22.1$ g, $p=0.02$) (Table A4). The association between T4 and birthweight unadjusted for perchlorate and creatinine was −0.24 g ($p=0.009$). The $\log_{10}$ perchlorate-birthweight linear regression coefficients unadjusted and adjusted for T4 were 149.8 ($p=0.01$) and 133.6 ($p=0.03$), respectively (Table A4), giving a Sobel value (“indirect effect”) of 16.2 ($p=0.05$) and suggesting a possible weak mediation effect. Further adjustments for maternal age, maternal weight, race, sex, or other factors had little impact on mediation results. The Sobel values for fT4 and $\log_{10}$ TSH were near 4.0 and not statistically significant (not shown). No evidence of mediation by T4, fT4 or TSH was seen for the elevated odds ratios in male births for perchlorate and preterm births >2500 g.

DISCUSSION

We identified an association between increasing maternal urinary perchlorate concentrations and increasing birthweight in male infants. Increasing perchlorate was associated with increases in the proportion of preterm births >2500 g in males and a corresponding decrease in the proportion of preterm births <2500 g in males. These latter findings are consistent with our birthweight analysis in which the largest perchlorate-increased male birthweight associations were seen in the analyses confined to pre-term births. Overall, these results suggest that perchlorate may increase male infant birthweight, particularly in infants born preterm.

An important strength of our study was the large size. With 1,957 subjects this is the largest study of perchlorate in pregnant women to date. Another important feature was the unique contamination situation in the study area which is likely at least partially responsible for the wide range of perchlorate exposure seen in our study subjects. Wide contrasts in exposure like this increase the likelihood that true associations can be identified with good statistical power. Another strength was our access to data on a large number of variables including race and ethnicity; birth and pregnancy complications; socioeconomic factors like maternal education and insurance type; anti-thyroid antibodies; and related chemicals including

cotinine, thiocyanate, nitrate, and iodine. These data allowed us to evaluate the potential confounding or modifying effects of a large number of factors that can potentially influence birth outcomes.

Only a few previous perchlorate studies have examined birth outcomes, and clear associations have not been seen (28–30). For example, in northern Chile, birthweights were similar in infants from cities with drinking water perchlorate concentrations of 113.9 μg/L (n=55 subjects), 5.82 μg/L (n=48), and below detection (n=55) although a large fraction of the subjects from the higher exposure city moved to and gave birth in the larger lower exposure city (30). In a recent study in New Jersey, maternal urinary perchlorate concentrations were not related to birthweight, although the sample size was small (n=107) and all subjects were recruited from a high risk pregnancy clinic (29). The study presented here is the first report of perchlorate exposure potentially altering birthweight, and the first to examine perchlorate and preterm birth.

The mechanisms that underlie our results are unknown. However, given the well-established mechanism linking high doses (e.g. 500–800 mg/day) of perchlorate to decreased thyroid iodide uptake and decreased thyroid hormone production, and the well-known role of thyroid hormone in fetal development, pathways involving this hormone seem most likely (31). Several studies have linked overt or subclinical hypothyroidism to increases in preterm birth, although findings are not consistent across all studies (25). Data linking thyroid function to changes in birthweight have also been inconsistent (25), although several results support the possibility that thyroid hormone could mediate our findings. For example, in the FASTER Trial of 10,990 births from throughout the US, first trimester hypothyroxinemia was associated with birthweights >4000 g (OR=1.97, 95% CI: 1.37–2.83) (32). In the Northern Finland Birth Cohort, clinical hypothyroidism (TSH >95th percentile) was associated with a greater ponderal index (28.4 vs. 27.6 kg/m^3, $p<0.05$) and greater mean birthweight (3676 vs. 3568 g) although the later was not statistically significant (33). In a study of all singleton births in Denmark from 1976–2006 (n=1,638,338) maternal hypothyroidism was associated with a 20 g (95% CI: 10–30 g) increase in birthweight and an odds ratio of 1.24 (95% CI: 1.17–1.31) for large-for-gestational age children (34). Other studies have not found clear associations between maternal hypothyroidism and birthweight (35, 36). Alterations in thyroid function have also been linked to gender-related effects on gonadal development, sex hormone and sex hormone binding globulin levels, and other outcomes (25), and it's possible one or more of these effects are related to the different results we identified in male versus female infants. As reported earlier, we found evidence that perchlorate decreases serum T4 and fT4 and increases serum TSH in the pregnant women in this cohort (8). In our analysis of mediation by T4 we also found evidence that decreasing serum T4 was associated with increasing birthweight (Table A3), highlighting the possibility that thyroid hormones could be mediating the perchlorate-birthweight associations we identified. Overall however, our mediation analyses suggested that T4 had only a weak mediating effect. Importantly though, this analysis was based on only a single assessment of thyroid hormone, levels of which change over the course of pregnancy and which have some day to day and within-day variability (25). In addition, pregnancy-related changes in serum proteins can impact the immunoassays we used to measure fT4 (37). As a

whole, these factors may have limited our ability to identify the true extent by which our results are mediated by thyroid hormones.

The magnitude of the perchlorate-birthweight association we identified for male infants was greater when mothers had lower (<100 μg/L) or higher (>300 μg/L) urinary iodide concentrations (Table 3). For those with lower urinary iodide levels, this finding is consistent with the known mechanism of perchlorate (iodide uptake inhibition in the thyroid) and the potential impacts of thyroid hormone on birthweight discussed above. In most individuals, very high iodine intakes can transiently and paradoxically inhibit thyroid hormone production, termed the acute Wolff-Chaikoff effect (38). Typically, this is only temporary and thyroid function returns to normal after a few days, even if high iodine exposure continues (39). However, several studies have reported increased rates of thyroid autoimmunity and hypothyroidism in areas where people have chronically high iodine intakes (40–44). This would suggest that chronic excessive high iodine intakes might lead to long-term hypothyroidism in some susceptible individuals. Although further research is needed on this issue, it may be that high iodine and perchlorate combine to reduce thyroid hormone production, and this combined exposure is responsible for the greater perchlorate-birthweight regression coefficient we saw in those with high urinary iodide levels.

The results of this study were also based on single assessments of urinary concentrations of perchlorate, iodide, thiocyanate, nitrate, and creatinine. All of these can also vary throughout the day and from day to day. The direction of any bias caused by this variability is unpredictable, however these variations would most likely reduce statistical power or bias any true associations to the null (45). The half-life of perchlorate excretion is fairly short (e.g., 48–72 hours) (46–48). However, a study in New York City children following urinary perchlorate levels over a six-month period has shown that a single measurement can be used to accurately classify participants into low, medium, and high long-term exposure groups (49). Overall, although our metric of perchlorate exposure likely involved some misclassification, this was unlikely to have caused the positive results we identified.

Our analyses incorporated several potential confounding factors known to influence birth outcomes, including maternal age, race and ethnicity, adverse pregnancy or birth conditions, or indicators of low socioeconomic status (SES) like maternal education or insurance payment method. None of these appeared to cause major confounding in our study. We did not have information on some of the other factors that may influence birth outcomes, including certain genetic conditions, diet (including consumption of foods like dairy products that can be high in perchlorate), some medications, or the presence of treated thyroid disease. Some of these factors, including the use of most medications during pregnancy or genetic abnormalities are likely too rare to cause major confounding. Overall, although we did not see evidence of major confounding, residual confounding or unknown confounding by factors we did not assess cannot be completely excluded.

Several of our findings varied by mother's birthplace. The exact reasons for this are unknown, although some of this may be related to some of the same issues influencing the *Hispanic paradox*, the phenomenon that despite lower socioeconomic status, Hispanic mothers born in Mexico who migrate to the US may have better pregnancy outcomes than

US-born mothers (50). Although the exact causes of this have not been clearly delineated possible explanations could be greater family or community support, diet, lower rates of smoking or alcohol intake, or fewer birth or delivery complications. In our study, US- and Mexico-born mothers differed on several factors including urinary thiocyanate levels and public insurance use (data not shown), however none of these factors was found to be an important effect modifier in the perchlorate-birthweight associations we identified. Overall, given the small sample sizes in some analyses and the multiple comparisons we performed, chance cannot be ruled out as an explanation for these birthplace differences. As such any conclusions based on these particular findings are speculative and these analyses should be replicated in larger detailed studies before any firm conclusions regarding perchlorate and mother's birthplace can be made.

In conclusion, we found evidence of association between perchlorate and male infant birthweight, particularly in preterm births. The long-term consequences of these associations are unknown. A number of previous studies have identified associations between increased birthweight overall and adult obesity, a well-known risk factor for several chronic adult diseases (51), as well as overall increased morbidity and mortality (52). Whether or not these findings are directly relevant to our results is currently unknown. Regardless these previous studies highlight the importance and potentially adverse impacts of any factor that may alter birthweight or any other birth outcome. Given the novelty of our findings, the fact that some sample sizes are small in some analyses, and that confounding or other bias cannot be ruled out, further research is needed in other populations, and these findings should be considered preliminary. However, because perchlorate exposure is ubiquitous, and because it can potentially impact thyroid function and fetal development, further research on this agent could have widespread public health importance.

Acknowledgments

This project was funded by grant R01ES020365 from the National Institute of Environmental Health Sciences (National Institutes of Health)

APPENDIX

Table A1

Distributions of perchlorate and other urinary analytes in pregnant women from San Diego County 2000–2003 and in reproductive-age women aged 15–45 years in the National Health and Nutrition Examination Survey (NHANES) 2001–2002

	San Diego study			NHANES		
Variable[1]	**N**	**Mean**	**IQR**	**N**	**Mean**	**IQR**
Urine perchlorate (μg/L)	1957	8.57	3.94–10.00	618	4.73	1.8–5.6
Urine thiocyanate (μg/L)	1957	1328	446–1580	617	2286	640–2600
Urine nitrate (mg/L)	1957	66.14	32.50–83.70	618	57.84	30.00–74.00
Urine iodide (μg/L)	1957	216.61	77.00–269.00	618	210.83	75.00–257.00
Urine creatinine (g/L)	1957	130.27	72.91–171.83	618	129.53	64.00–177.00

Abbreviations: N, number of participants; IQR, interquartile range

[1] Urinary concentrations are not corrected for urinary creatinine concentration

Table A2

Sociodemographic variables of the included and excluded subjects in the study population of pregnant women from San Diego County 2000–2003

Variable	Category	Included N (%)	Excluded N (%)
All subjects		1957 (100%)	227 (100%)
Sex	Female	998 (51.0%)	112 (49.3%)
	Male	959 (49.0%)	115 (50.7%)
Race/ethnicity	Hispanic	1352 (69.1%)	171 (75.3%)
	Asian	25 (1.3%)	3 (1.3%)
	Black	81 (4.1%)	6 (2.6%)
	Other	90 (4.6%)	8 (3.5%)
	White	409 (20.9%)	39 (17.2%)
Mother's birthplace	US	882 (45.1%)	98 (43.2%)
	Mexico	933 (47.7%)	115 (50.7%)
	Other	142 (7.3%)	14 (6.2%)
Maternal age (years)	<21	446 (22.8%)	54 (23.8%)
	21–25	575 (29.4%)	59 (26.0%)
	26–30	435 (22.2%)	61 (26.9%)
	>30	501 (25.6%)	53 (23.3%)
Maternal education (highest grade)	<9	537 (28.0%)	63 (28.3%)
	9–11	319 (16.6%)	38 (17.0%)
	12	580 (30.2%)	74 (33.2%)
	>12	484 (25.2%)	48 (21.5%)
Maternal weight (lbs)	<130	441 (25.0%)	55 (24.2%)
	131–147	438 (24.8%)	37 (16.3%)
	148–160	449 (25.4%)	78 (34.4%)
	>160	438 (24.8%)	57 (25.1%)
Delivery	NVD	1523 (77.8%)	161 (70.9%)
	Caesarean	434 (22.2%)	66 (29.1%)
Insurance	Private	589 (30.1%)	68 (30.1%)
	Public	1368 (69.9%)	158 (69.9%)

Abbreviations: N, number of participants; NVD, normal vaginal delivery

Table A3

Mean birthweight (grams) by quartiles of perchlorate concentrations in male births from US born mothers in the study population of pregnant women from San Diego County 2000–2003 (p-trend in mean birthweights across quartiles=0.009)

Perchlorate (μg/L)[1]	N	Birthweight[2]	95% CI	p-value[3]
0.82–4.71	111	3402.5	3303.1–3502.0	Reference
4.72–6.89	111	3461.6	3362.7–3560.4	0.41
6.90–10.15	112	3563.6	3465.4–3661.8	0.02
10.25–86.83	111	3566.8	3467.8–3665.8	0.02

Abbreviations: CI, confidence interval; N, sample size

[1]Unadjusted for urinary creatinine concentration

[2]Adjusted means, adjusted for maternal age, maternal weight, urinary creatinine (log10), and race

[3]p-value compared to the lowest quartile

Table A4

Results of the mediation analysis of maternal serum total thyroxine (T4) on the association between maternal urine perchlorate and birthweight in male infants (n=862) in the study population of pregnant women from San Diego County 2000–2003[1]

Model	Dependent variable	Independent variables	β	SE	p-value
MODEL 1	T4	Log_{10} perchlorate	−0.73	0.22	0.0008
MODEL 2[2]	Birthweight	Log_{10} perchlorate	133.6	60.4	0.03
		T4	−22.1	9.4	0.02
MODEL 3	Birthweight	Log_{10} perchlorate	149.8	60.2	0.01

[1]All models adjusted for urinary creatinine (log10). All models include the same 862 male subjects with information on perchlorate, creatinine, and maternal T4

[2]This model includes both log_{10} perchlorate and serum T4

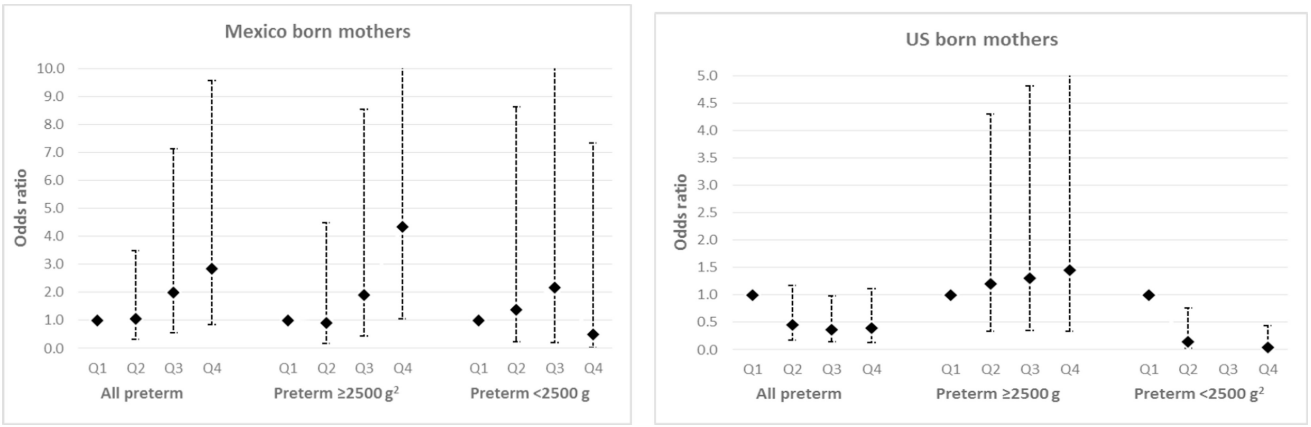

Figure A1.

Odds ratio of preterm birth by urinary maternal perchlorate concentration quartiles (Q1-Q4) in male infants of Mexico and US born mothers in the study population of pregnant women from San Diego County 2000–2003[1]

1. Lowest quartile of unadjusted maternal urinary perchlorate concentration (Q1) is used as the reference group. Odds ratios are for preterm birth compared to all other births (i.e. all term and post-term births). ORs are adjusted for creatinine (log10), maternal age, maternal weight, and race

2. p-trend <0.05

For US born mothers there were no cases of preterm births <2500 g in third perchlorate quartile

References

1. Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, et al. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect. 2006; 114(12):1865–71. [PubMed: 17185277]
2. Tonacchera M, Pinchera A, Dimida A, Ferrarini E, et al. Relative potencies and additivity of perchlorate, thiocyanate, nitrate, and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter. Thyroid. 2004; 14(12):1012–9. [PubMed: 15650353]
3. Haddow JE, Palomaki GE, Allan WC, Williams JR, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 1999; 341(8):549–55. [PubMed: 10451459]
4. Pop VJ, Brouwers EP, Vader HL, Vulsma T, et al. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf). 2003; 59(3):282–8. [PubMed: 12919150]
5. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf). 1999; 50(2):149–55. [PubMed: 10396355]
6. Henrichs J, Ghassabian A, Peeters RP, Tiemeier H. Maternal hypothyroxinemia and effects on cognitive functioning in childhood: how and why? Clin Endocrinol (Oxf). 2013; 79(2):152–62. [PubMed: 23600900]
7. Miller MD, Crofton KM, Rice DC, Zoeller RT. Thyroid-disrupting chemicals: interpreting upstream biomarkers of adverse outcomes. Environ Health Perspect. 2009; 117(7):1033–41. [PubMed: 19654909]
8. Steinmaus C, Pearl M, Kharrazi M, Blount BC, et al. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in southern California. Environ Health Perspect. 2015; 124:861–7. [PubMed: 26485730]
9. U.S. EPA. Perchlorate monitoring results. Henderson, Nevada to the lower Colorado River. 2005. Available from: http://www.epa.gov/fedfac/pdf/perrpt12_05.pdf
10. Steinmaus C, Miller MD, Howd R. Impact of smoking and thiocyanate on perchlorate and thyroid hormone associations in the 2001-2002 National Health and Nutrition Examination Survey. Environ Health Perspect. 2007; 115(9):1333–8. [PubMed: 17805424]
11. Heck JE, Park AS, Contreras ZA, Davidson TB, et al. Risk of childhood cancer by maternal birthplace: a test of the Hispanic paradox. JAMA Pediatr. 2016; 170(6):585–92. [PubMed: 27110958]
12. United Nations Development Programme. UNDP Environment and Energy Group. Energy and Environment Practice Gender Mainstreaming Guidance Series Chemicals Management. Chemicals and Gender. 2011. Available from: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwjx6tWTlMjNAhVJWD4KHaidAcYQFggmMAA&url=http%3A%2F%2Fwww.undp.org%2Fcontent%2Fdam%2Faplaws%2Fpublication%2Fen%2Fpublications%2Fenvironment-energy%2Fwww-ee-library%2Fchemicals-management%2Fchemicals-andgender%2F2011%2520Chemical%26Gender.pdf&usg=AFQjCNFM_7jcDJUs9l5394VLd2mbjvdApg&sig2=wbbaguIj0qNHr0tZb6UKGQ
13. Stetson SJ, Wanty RB, Helsel DR, Kalkhoff SJ, et al. Stability of low levels of perchlorate in drinking water and natural water samples. Anal Chim Acta. 2006; 567(1):108–13. [PubMed: 17723386]
14. Blount BC, Valentin-Blasini L, Osterloh JD, Mauldin JP, et al. Perchlorate exposure of the US population, 2001-2002. J Expo Sci Environ Epidemiol. 2007; 17(4):400–7. [PubMed: 17051137]
15. California Department of Public Health. California Newborn Screening Program. 2010. Available from: http://www.cdph.ca.gov/programs/NBS/Pages/default.aspx
16. Mannisto T, Surcel HM, Bloigu A, Ruokonen A, et al. The effect of freezing, thawing, and short- and long-term storage on serum thyrotropin, thyroid hormones, and thyroid autoantibodies: implications for analyzing samples stored in serum banks. Clin Chem. 2007; 53(11):1986–7. [PubMed: 17954505]

17. Dietz PM, England LJ, Callaghan WM, Pearl M, et al. A comparison of LMP-based and ultrasound-based estimates of gestational age using linked California livebirth and prenatal screening records. Paediatr Perinat Epidemiol. 2007; 21(Suppl 2):62–71. [PubMed: 17803619]
18. Pearl M, Wier ML, Kharrazi M. Assessing the quality of last menstrual period date on California birth records. Paediatr Perinat Epidemiol. 2007; 21(Suppl 2):50–61. [PubMed: 17803618]
19. Kharrazi M, Pearl M, Yang J, DeLorenze GN, et al. California Very Preterm Birth Study: design and characteristics of the population- and biospecimen bank-based nested case-control study. Paediatr Perinat Epidemiol. 2012; 26(3):250–63. [PubMed: 22471684]
20. Blount BC, Valentin-Blasini L. Biomonitoring as a method for assessing exposure to perchlorate. Thyroid. 2007; 17(9):837–41. [PubMed: 17822374]
21. Valentin-Blasini L, Blount BC, Delinsky A. Quantification of iodide and sodium-iodide symporter inhibitors in human urine using ion chromatography tandem mass spectrometry. J Chromatogr A. 2007; 1155(1):40–6. [PubMed: 17466997]
22. Caudill SP, Schleicher RL, Pirkle JL. Multi-rule quality control for the age-related eye disease study. Stat Med. 2008; 27(20):4094–106. [PubMed: 18344178]
23. WHO. Assessment of iodine deficieny disorders and monitoring their elimination: a guide for Programme managers. 3. World Health Organization; Geneva: 2007.
24. Markides KS, Coreil J. The health of Hispanics in the southwestern United States: an epidemiologic paradox. Public Health Rep. 1986; 101(3):253–65. [PubMed: 3086917]
25. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev. 2010; 31(5):702–55. [PubMed: 20573783]
26. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods. 2013; 18(2):137–50. [PubMed: 23379553]
27. Yerushalmy J. The classification of newborn infants by birth weight and gestational age. J Pediatr. 1967; 71(2):164–72. [PubMed: 6029464]
28. Blount BC, Rich DQ, Valentin-Blasini L, Lashley S, et al. Perinatal exposure to perchlorate, thiocyanate, and nitrate in New Jersey mothers and newborns. Environ Sci Technol. 2009; 43(19): 7543–9. [PubMed: 19848174]
29. Evans KA, Rich DQ, Weinberger B, Vetrano AM, et al. Association of prenatal perchlorate, thiocyanate, and nitrate exposure with neonatal size and gestational age. Reprod Toxicol. 2015; 57:183–9. [PubMed: 26169551]
30. Tellez Tellez R, Michaud Chacon P, Reyes Abarca C, Blount BC, et al. Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. Thyroid. 2005; 15(9):963–75. [PubMed: 16187904]
31. Leung AM, Pearce EN, Braverman LE. Perchlorate, iodine and the thyroid. Best Pract Res Clin Endocrinol Metab. 2010; 24(1):133–41. [PubMed: 20172477]
32. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, et al. Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol. 2008; 112(1):85–92. [PubMed: 18591312]
33. Mannisto T, Vaarasmaki M, Pouta A, Hartikainen AL, et al. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. J Clin Endocrinol Metab. 2009; 94(3):772–9. [PubMed: 19106271]
34. Andersen SL, Olsen J, Wu CS, Laurberg P. Low Birth Weight in Children Born to Mothers with Hyperthyroidism and High Birth Weight in Hypothyroidism, whereas Preterm Birth Is Common in Both Conditions: A Danish National Hospital Register Study. Eur Thyroid J. 2013; 2(2):135–44. [PubMed: 24783052]
35. Casey BM, Dashe JS, Wells CE, McIntire DD, et al. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol. 2005; 105(2):239–45. [PubMed: 15684146]
36. Finken MJ, van Eijsden M, Loomans EM, Vrijkotte TG, et al. Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring. J Clin Endocrinol Metab. 2013; 98(4):1417–26. [PubMed: 23408575]
37. Lee RH, Spencer CA, Mestman JH, Miller EA, et al. Free T4 immunoassays are flawed during pregnancy. Am J Obstet Gynecol. 2009; 200(3):260, e1–6. [PubMed: 19114271]

38. Wolff J, Chaikoff I. Plasma inorganic iodide as a homeostatic regulator of thyroid function. J Biological Chem. 1948; 174:555–564.
39. Eng PH, Cardona GR, Fang SL, Previti M, et al. Escape from the acute Wolff-Chaikoff effect is associated with a decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein. Endocrinology. 1999; 140(8):3404–10. [PubMed: 10433193]
40. Konno N, Makita H, Yuri K, Iizuka N, et al. Association between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan. J Clin Endocrinol Metab. 1994; 78(2):393–7. [PubMed: 8106628]
41. Pedersen IB, Laurberg P, Knudsen N, Jorgensen T, et al. An increased incidence of overt hypothyroidism after iodine fortification of salt in Denmark: a prospective population study. J Clin Endocrinol Metab. 2007; 92(8):3122–7. [PubMed: 17504896]
42. Tajiri J, Higashi K, Morita M, Umeda T, et al. Studies of hypothyroidism in patients with high iodine intake. J Clin Endocrinol Metab. 1986; 63(2):412–7. [PubMed: 3722332]
43. Teng W, Shan Z, Teng X, Guan H, et al. Effect of iodine intake on thyroid diseases in China. N Engl J Med. 2006; 354(26):2783–93. [PubMed: 16807415]
44. Li M, Liu DR, Qu CY, Zhang PY, et al. Endemic goitre in central China caused by excessive iodine intake. Lancet. 1987; 2(8553):257–9. [PubMed: 2886725]
45. Roy T. Fitting a straight line when both variables are subject to error: pharmaceutical applications. J Pharm Biomed Anal. 1994; 12(10):1265–9. [PubMed: 7841221]
46. Greer MA, Goodman G, Pleus RC, Greer SE. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. Environ Health Perspect. 2002; 110(9):927–37. [PubMed: 12204829]
47. Lamm SH, Braverman LE, Li FX, Richman K, et al. Thyroid health status of ammonium perchlorate workers: a cross-sectional occupational health study. J Occup Environ Med. 1999; 41(4):248–60. [PubMed: 10224590]
48. Selivanova L, Arefaeva Z. The dynamics behind the absorption and elimination of perchloric acid salts in laboratory animals and agricultural livestock. Chemistry P.S.X. 1986; 24:43–45.
49. Mervish N, Blount B, Valentin-Blasini L, Brenner B, et al. Temporal variability in urinary concentrations of perchlorate, nitrate, thiocyanate and iodide among children. J Exp Sci Environ Epidemiol. 2011; 22(2):212–8.
50. DeCamp LR, Choi H, Fuentes-Afflick E, Sastry N. Immigrant Latino neighborhoods and mortality among infants born to Mexican-origin Latina women. Matern Child Health J. 2015; 19(6):1354–63. [PubMed: 25430802]
51. Schellong K, Schulz S, Harder T, Plagemann A. Birth weight and long-term overweight risk: systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally. PLoS One. 2012; 7(10):e47776. [PubMed: 23082214]
52. Van den Berg BJ, Yerushalmy J. The relationship of the rate of intrauterine growth of infants of low birth weight to mortality, morbidity, and congenital anomalies. J Pediatr. 1966; 69(4):531–45. [PubMed: 5950867]
53. Alexander EK, Pearce EN, Brent GA, Brown RS, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017; 27(3):315–389. [PubMed: 28056690]

Highlights

- Perchlorate was associated with increased birth weight in male infants.
- Perchlorate-birth weight associations were greater for US- vs. Mexico-born mothers.
- Perchlorate was associated with increased preterm births ≥2500g in male infants.

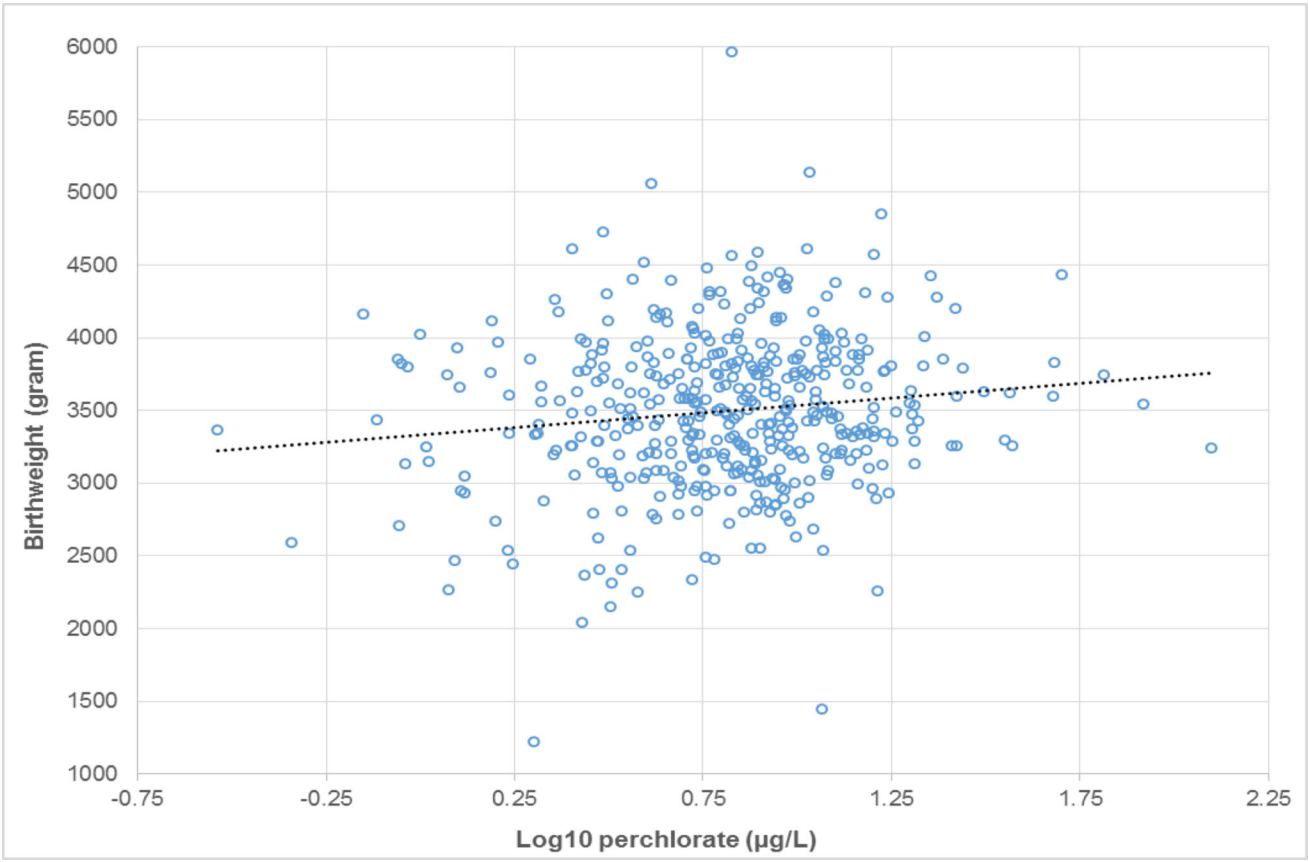

Figure 1.

Log_{10} maternal urinary perchlorate concentrations and birthweight in male infants of US born mothers (regression coefficient between birthweight and log10 perchlorate = 297.2 g, p <0.001) in the study population of pregnant women from San Diego County 2000–2003 The dotted line represents the trend calculated using linear regression.

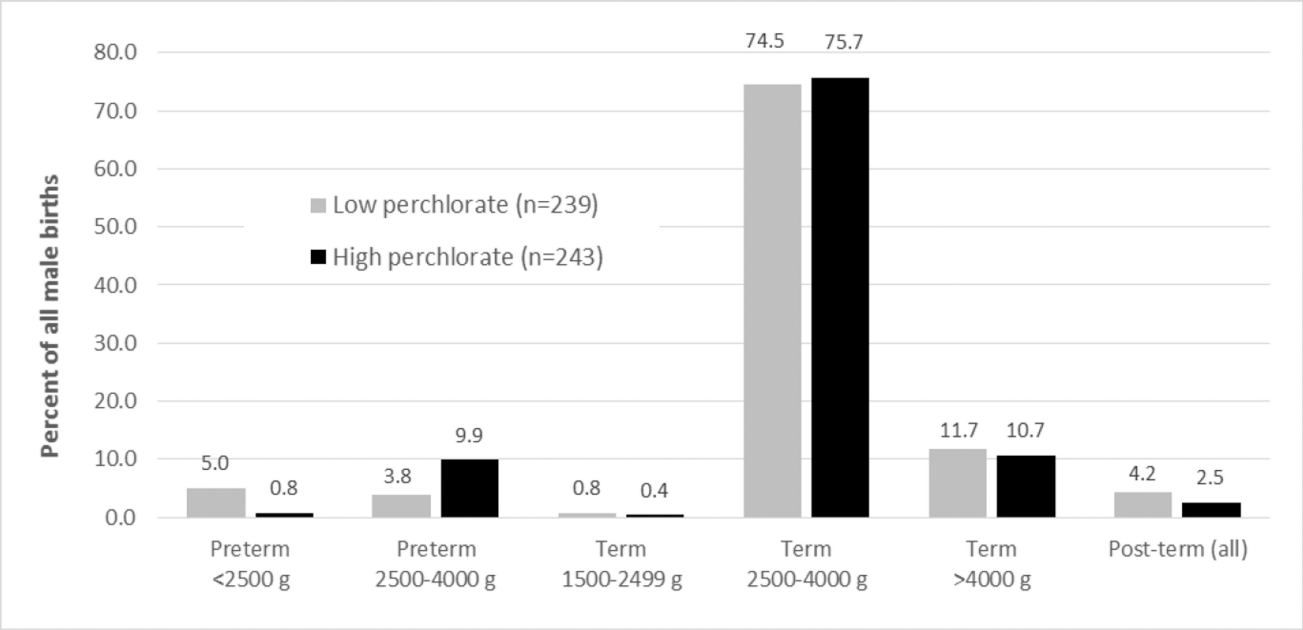

Figure 2.

Proportions of male births in various birthweight-gestational age categories (27), comparing infants of mothers with high and low urinary perchlorate concentrations in the study population of pregnant women from San Diego County 2000–2003

The high and low perchlorate groups are the upper (range: 10.0–177.0 μg/L, unadjusted for urinary creatinine concentration) and lower (range: 0.23–3.94 μg/L, unadjusted for urinary creatinine concentration) quartiles in all subjects, respectively. Some groups are not displayed because of small numbers.

Table 1

Distributions of perchlorate, other urinary analytes, serum thyroid hormones, and other factors in pregnant women from San Diego County 2000–2003

					Percentiles			
Variable	**N**	**Mean**	**SD**	**Min**	**25th**	**50th**	**75th**	**Max**
Urine perchlorate (μg/L)[2]	1957	8.57	9.99	0.23	3.94	6.50	10.00	177.00
Urine thiocyanate (μg/L)[2]	1957	1328	1519	20	446	881	1580	16200
Urine nitrate (mg/L)[2]	1957	66.14	57.71	0.70	32.50	54.80	83.70	796.00
Urine iodide (μg/L)[2]	1957	216.61	256.81	0.81	77.00	153.00	269.00	3330.00
Urine creatinine (g/L)	1957	130.27	75.04	7.90	72.91	119.37	171.83	472.46
Birthweight (gm)	1957	3418	521	610	3130	3430	3742	5970
Gestational age (weeks)	1957	39.32	1.87	23.00	38.57	39.57	40.43	46.14
Maternal age (years)	1957	25.57	5.74	14.00	21.00	25.00	30.00	43.00
T4 (μg/dl)[1]	1766	12.31	1.87	0.56	11.21	12.26	13.39	19.99
TSH (μIU/mL)[1]	1765	1.36	0.86	0.00	0.81	1.20	1.69	8.39
fT4 (ng/dL)[a]	1766	0.86	0.19	0.11	0.77	0.85	0.93	5.44

Abbreviations: fT4, free thyroxine; Max, maximum; Min, minimum; N, number of participants; SD, standard deviation; T4, total thyroxine; TSH, thyroid stimulating hormone

[1] Reference ranges from the University of Washington for all ages and genders are: 4.8–10.8 μg/dL for total T4; 0.6–1.2 ng/dL for fT4 and 0.4–5.0 μIU/mL for TSH. The American Thyroid Association upper reference range for TSH in second trimester pregnancy is 4.0 μIU/mL (53).

[2] Urinary concentrations are not corrected for urinary creatinine concentration

Table 2

Mean maternal urinary perchlorate concentrations (μg/L) and birthweights (grams), and percentage preterm births by categories of various sociodemographic characteristics in the study population of pregnant women from San Diego County 2000–2003

Variable	Category	Category N (%)[1]	Perchlorate[2] Mean (SD)	Birthweight Mean (SD)	Preterm N (%)[3]
All subjects		1957 (100%)	8.57 (9.99)	3418.3 (520.7)	158 (8.1%)
Sex	Female	998 (51.0%)	8.49 (10.48)	3341.4 (519.5)	73 (7.3%)
	Male	959 (49.0%)	8.66 (9.47)	3498.2 (510.0)	85 (8.9%)
Race/ethnicity	Hispanic	1352 (69.1%)	8.42 (10.36)	3426.8 (519.3)	104 (7.7%)
	Asian	25 (1.3%)	9.65 (14.12)	3477.8 (549.7)	3 (12.0%)
	Black	81 (4.1%)	11.85 (15.28)	3278.8 (503.1)	9 (11.1%)
	Other	90 (4.6%)	6.81 (4.75)	3240.1 (527.6)	9 (10.0%)
	White	409 (20.9%)	8.73 (7.63)	3453.2 (515.8)	33 (8.1%)
Mother's birthplace	US	882 (45.1%)	8.90 (10.35)	3424.9 (533.4)	78 (8.8%)
	Mexico	933 (47.7%)	8.40 (10.03)	3422.9 (508.2)	70 (7.5%)
	Other	142 (7.3%)	7.63 (6.98)	3347.2 (520.3)	10 (7.0%)
Maternal age (years)	<21	446 (22.8%)	7.68 (7.51)	3348.7 (491.5)	32 (7.2%)
	21–25	575 (29.4%)	8.99 (11.18)	3423.6 (487.6)	36 (6.3%)
	26–30	435 (22.2%)	9.12 (12.96)	3442.1 (534.3)	36 (8.3%)
	>30	501 (25.6%)	8.39 (7.07)	3453.4 (564.6)	54 (10.8%)
Maternal education (highest grade)	<9	537 (28.0%)	8.52 (9.24)	3440.5 (493.6)	34 (6.3%)
	9–11	319 (16.6%)	8.70 (11.59)	3375.8 (532.0)	29 (9.1%)
	12	580 (30.2%)	8.69 (11.02)	3400.2 (532.8)	54 (9.3%)
	>12	484 (25.2%)	8.43 (8.50)	3441.9 (534.3)	39 (8.1%)
Maternal weight (lbs)	<130	441 (25.0%)	7.78 (8.12)	3243.4 (459.1)	31 (7.0%)
	131–147	438 (24.8%)	8.10 (10.01)	3358.0 (463.4)	33 (7.5%)
	148–160	449 (25.4%)	9.41 (13.15)	3478.2 (497.9)	33 (7.3%)
	>160	438 (24.8%)	8.86 (8.10)	3584.7 (591.0)	38 (8.7%)
Delivery	NVD	1523 (77.8%)	8.66 (10.55)	3400.5 (487.6)	119 (7.8%)
	Caesarean	434 (22.2%)	8.25 (7.73)	3480.5 (619.8)	39 (9.0%)
Insurance	Private	589 (30.1%)	8.58 (10.31)	3429.2 (507.5)	41 (7.0%)
	Public	1368 (69.9%)	8.57 (9.86)	3413.6 (526.4)	117 (8.6%)

Abbreviations: N, number of participants; NVD, normal vaginal delivery; SD, standard deviation

[1] Percentage of all births in this category

[2] Urinary perchlorate concentrations are not corrected for urinary creatinine concentration

[3] Percentage of all births in this category that were preterm

Table 3

Regression coefficients between maternal $\log_{10}$ urine perchlorate concentrations (μg/L) and birthweight (grams) in the study population of pregnant women from San Diego County 2000–2003

	Both sexes				Males				Females			
Group	**N**	**β[1]**	**SE**	**p**	**N**	**β[1]**	**SE**	**p**	**N**	**β[1]**	**SE**	**p**
All	1957	51.3	39.7	0.20	959	143.1	56.3	0.01	998	−38.3	56.0	0.49
Urinary iodide[2]												
<100 μg/L	629	87.2	68.2	0.20	313	177.3	91.7	0.05	316	−14.8	102.1	0.88
100–300 μg/L	920	−34.7	57.8	0.55	444	25.4	84.6	0.76	476	−84.6	79.6	0.29
>300 μg/L	408	185.2	113.3	0.10	202	301.1	161.5	0.06	206	−1.1	160.1	0.99
Gestational age												
<37 weeks	158	547.3	202.6	0.01	85	829.1	263.1	<0.001	73	230.4	319.1	0.47
≥37 weeks	1799	28.8	36.0	0.42	874	97.3	51.5	0.06	925	−39.5	50.2	0.43
Mothers	birthplace											
Mexico	933	27.1	53.1	0.61	451	29.9	72.6	0.68	482	26.0	77.8	0.74
US born												
All	882	95.3	63.0	0.13	445	297.2	91.9	<0.001	437	−95.1	86.4	0.27
White	381	166.7	104.9	0.11	204	325.6	151.4	0.03	177	−34.8	144.7	0.81
Hispanic	394	40.4	94.7	0.67	186	305.4	136.9	0.03	208	−186.0	129.3	0.15
Other	107	137.3	144.4	0.34	55	408.3	202.5	0.05	52	−43.2	184.2	0.82
Other birthplace	142	−39.0	167.9	0.82	63	23.8	255.6	0.93	79	−115.8	237.1	0.63

Abbreviations: β, regression coefficient; N, sample size; SE, standard error

[1] Adjusted for urinary creatinine (log10), maternal age, maternal weight, race, and sex

[2] Urinary iodide concentrations were not corrected for urinary creatinine concentrations

Table 4

Odds ratios for preterm birth by quartile of maternal urinary perchlorate concentration in the study population of pregnant women from San Diego County 2000–2003

		Both sexes						Males						Females					
Group	**Perc quart.**	**Cases**	**Cont**	**OR[1]**	**95% CI L**	**95% CI U**	**p-trend**	**Cases**	**Cont**	**OR[1]**	**95% CI L**	**95% CI U**	**p-trend**	**Cases**	**Cont**	**OR[1]**	**95% CI L**	**95% CI U**	**p-trend**
All preterm births:																			
	1	36	452	1.00	Ref			21	218	1.00	Ref			15	234	1.00	Ref		
	2	33	458	0.86	0.51	1.45		17	220	0.77	0.38	1.56		16	238	0.94	0.43	2.04	
	3	43	447	1.09	0.64	1.85		21	219	0.86	0.41	1.82		22	228	1.30	0.60	2.82	
	4	46	442	1.11	0.64	1.92	0.72	26	217	1.14	0.53	2.45	0.73	20	225	1.06	0.47	2.38	0.90
Preterm ≥2500 g:																			
	1	19	469	1.00	Ref			9	230	1.00	Ref			10	239	1.00	Ref		
	2	22	469	1.09	0.56	2.11		12	225	1.39	0.54	3.57		10	244	0.86	0.33	2.22	
	3	33	457	1.53	0.79	2.99		19	221	1.82	0.69	4.80		14	236	1.22	0.47	3.13	
	4	37	451	1.84	0.91	3.72	0.09	24	219	3.03	1.09	8.40	0.03	13	232	1.07	0.39	2.89	0.90
Preterm <2500 g:																			
	1	17	471	1.00	Ref			12	227	1.00	Ref			5	244	1.00	Ref		
	2	11	480	0.62	0.27	1.39		5	232	0.37	0.12	1.12		6	248	1.11	0.30	4.08	
	3	10	480	0.57	0.23	1.39		2	238	0.16	0.03	0.79		8	242	1.44	0.40	5.21	
	4	9	479	0.42	0.16	1.06	0.07	2	241	0.12	0.02	0.61	0.01	7	238	1.06	0.28	3.97	0.94

Abbreviations: CI_L, lower confidence interval; CI_U, upper confidence interval; Cont, controls; OR, odds ratio; Perc quart, maternal urinary perchlorate concentration quartile unadjusted for urinary creatinine concentrations (cut-off points are 3.94, 6.50, and 10.0 μg/L); Ref, Reference category

[1]Adjusted for creatinine (log10), maternal age, maternal weight, race, (and sex, for analyses of both sexes)