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Environmental Perchlorate and Thiocyanate Exposures and Infant Serum Thyroid Function

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Background: Breastfed infants rely on maternal iodine for thyroid hormone production required for neurodevelopment. Dietary iodine among women of childbearing age in the United States may be insufficient. Perchlorate (competitive inhibitor of the sodium/iodide symporter [NIS]) exposure is ubiquitous. Thiocyanate, from cigarettes and diet, is a weaker NIS inhibitor. Environmental perchlorate and thiocyanate exposures could decrease breast milk iodine by competitively inhibiting NIS in lactating breasts (thus impairing infants' iodine availability), and/or infants' thyroidal NIS to directly decrease infant thyroid function. The current study assessed the relationships between environmental perchlorate and thiocyanate exposures and infant serum thyroid function.

Methods: Iodine, perchlorate, and thiocyanate in breast milk, maternal and infant urine, and infant serum thyroid function tests were cross-sectionally measured in Boston-area women and their 1–3 month-old breastfed infants. Univariate and multivariable analyses assessed relationships between iodine, perchlorate, thiocyanate, thyroid-stimulating hormone (TSH), and free thyroxine (FT4) levels.

Results: In 64 mothers and infants, median (range) iodine levels were 45.6 μg/L (4.3–1080) in breast milk, 101.9 μg/L (27–570) in maternal urine, and 197.5 μg/L (40–785) in infant urine. Median perchlorate concentrations were 4.4 μg/L (0.5–29.5) in breast milk, 3.1 μg/L (0.2–22.4) in maternal urine, and 4.7 μg/L (0.3–25.3) in infant urine. There were no correlations between infant TSH or FT4 and iodine, perchlorate, and thiocyanate levels in breast milk, maternal urine, and infant urine. In multivariable analyses, perchlorate and thiocyanate levels in breast milk, maternal urine, and infant urine were not significant predictors of infant TSH or FT4.

Conclusions: Boston-area mothers and their breastfed infants are generally iodine sufficient. Although environmental perchlorate and thiocyanate are ubiquitous, these results do not support the concern that maternal and infant environmental perchlorate and thiocyanate exposures affect infant thyroid function.

Introduction

Normal thyroid function depends on sufficient dietary iodine intake. Breastfed infants rely on maternal dietary iodine for their iodine nutrition and thyroid hormone production, both of which are crucial for normal neurodevelopment. Pregnant women and their developing fetuses and infants are thus the most susceptible groups for even very subtly inadequate iodine nutrition and mild hypothyroidism. As such, dietary iodine requirements are increased in lactation. The Institute of Medicine's Recommended Dietary Allowance (RDA) for dietary iodine intake is 290 μg/day for lactating women, higher than the 150 μg/day recommended for nonpregnant adults and 220 μg/day for pregnant women (1).

There has been recent concern that low-level exposures to certain environmental agents may have potentially adverse effects on iodine utilization and thyroid function. Perchlorate, a component of solid rocket fuel, fireworks, and other explosives, is found in some crop fertilizers formerly used in the United States, and is produced by natural processes (2). It is a competitive inhibitor of the sodium/iodide symporter (NIS), which actively transports iodine into thyroid and lactating mammary cells (3). In pharmacological doses, perchlorate decreases the active transport of iodine into the thyroid and possibly breast milk (4) by competitively inhibiting NIS at 30 times the affinity for iodide (5). Furthermore, recent studies in lactating mice have suggested that perchlorate is actively transported into breast milk (6). Environmental perchlorate

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exposure could thus potentially decrease breast milk iodine levels and infants' thyroid hormone synthesis.

Cigarette smoke contains cyanide that is metabolized to thiocyanate, which can also decrease the uptake of iodine into the thyroid and breast milk by competitively inhibiting NIS, although thiocyanate is a far less potent NIS competitor than perchlorate (5). Thiocyanate is also naturally found in Brassica genus vegetables, such as cauliflower, broccoli, kale, and Brussel sprouts. Thiocyanate decreases breast milk iodine concentrations (7,8), and may thus exacerbate the effects of environmental perchlorate exposure on thyroid function in breastfed infants.

The objective of the present study was to cross-sectionally assess the relationships between environmental perchlorate, thiocyanate exposures, dietary iodine nutrition (as measured by breast milk and maternal and urinary iodine concentrations), and infant serum thyroid function among Boston-area women and their breastfed infants.

Methods

Subjects

The Boston University Medical Campus Institutional Review Board (IRB) approved the protocol, and informed consent was obtained. We recruited 64 breastfed 1–3-month-old infants and their mothers (total $n = 128$) from the Boston Medical Center between November 2008 and May 2011. Mothers were ≥18 years old, and infants were delivered full-term (≥37 weeks gestation) and either exclusively or partially breastfed. Exclusion criteria for both mothers and infants were a history of thyroid disease, thyroid hormone use, recent exposure to iodine-containing medications and contrast agents, and, for mothers, inability to understand English.

During the study period, 1563 infants were scheduled for a routine pediatric visit at our hospital. We were unable to achieve our targeted enrollment of 275 mother–infant pairs due to various exclusion criteria ($n = 759$); 593 were non-breastfed infants, 131 were premature infants, 25 had either maternal or infant thyroid disease, and 10 infants were accompanied to the visit by only the father. Other reasons for not enrolling subjects were failure to appear for the pediatric well-baby visits ($n = 294$), mother's decision to decline study participation ($n = 177$), non-English-speaking mothers ($n = 141$), the arrival of the mother and infant at other than the scheduled appointment time ($n = 65$), visit cancellation ($n = 58$), logistical issues related to IRB study renewal ($n = 4$), and refusal of research study participation by the infant's pediatrician ($n = 1$). Thus, the reported sample size in this study is 64 women and their infants.

Recruited mothers completed a questionnaire to provide information regarding their age, ethnicity, birthplace, highest level of education, marital status, prenatal multivitamin use, cigarette smoking, and brand name and estimated daily average of any supplemental infant formula use. The majority of enrolled mothers in our study sample (65%) supplemented their infants with an infant formula.

Laboratory measurements

Samples of breast milk, maternal urine, infant urine, and infant serum were collected from mothers and their infants within the same hour, except in one infant whose serum was collected 47 hours after breast milk, maternal urine, and infant urine were obtained. Levels of breast milk and urinary iodine, perchlorate and thiocyanate were measured by ion chromatography–mass spectrometry (9). The limit of detection for perchlorate is 0.05 μg/L, and the interassay coefficient of variation for this method in our laboratory ranges from 2.2%–5.9%. The limit of detection for thiocyanate is 0.5 μg/L, and the interassay coefficient of variation for this method in our laboratory is <5%. Enzyme-linked immunosorbent assay (ELISA) was used to measure infant serum thyroid-stimulating hormone (TSH) (normal range: 0.6–5.5 mIU/L) and free thyroxine (FT4) (normal range: 0.8–2.2 ng/dL) (Immuno-Biological Laboratories, Inc., Minneapolis, MN).

Statistical analysis

Descriptive statistics are reported for breast milk and urinary iodine, perchlorate, thiocyanate, and serum thyroid function concentrations. Median urinary iodine concentrations are compared to recent World Health Organization (WHO) guidelines (10). Serum TSH values were non-normally distributed and logarithmically transformed for multivariable analyses. Sample size determination (target of 275 mothers and their infants; total $n = 550$) was based on the ability to have 90% power to see a model R^2 of 5% using multivariable linear regression containing three predictors of infant thyroid function.

Spearman's correlation coefficients were used to examine the associations between breast milk and urinary iodine, perchlorate, thiocyanate, and serum TSH and FT4 levels. Multivariable linear regression models were used to determine significant predictors of infant thyroid function and adjusted for important covariates, confounders, and effect modifiers. The regression model for perchlorate was adjusted for thiocyanate exposure, and the regression model for thiocyanate was adjusted for perchlorate exposure. The models were adjusted for maternal age, ethnicity (in the National Health and Nutrition Examination Survey [NHANES] 2001–2002, non-Hispanic blacks had lower urinary perchlorate levels than non-Hispanic whites) (11), self-reported smoking behavior, iodine-containing multivitamin use, and supplemental infant formula use. Supplemental infant formula use was assessed as a categorical measure of estimated daily use. All statistical tests were considered significant if the two-tailed p-value was < 0.05. Data processing and statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Descriptive characteristics of the subjects are shown in Table 1. Mean maternal age was 28.7 ± 7.9 (SD) years. Mothers were primarily single, black women not born in the United States who had achieved no higher than a high school education, took a daily prenatal multivitamin, and were non-smokers. The median (range) breast milk iodine level was 45.6 μg/L (4.3–1080 μg/L). Median (range) iodine levels in maternal urine (101.9 μg/L [27–570 μg/L]) were significantly lower than in infant urine (197.5 μg/L [40–785 μg/L]) ($p < 0.01$). Median (range) perchlorate concentrations were 4.4 μg/L (0.5–29.5 μg/L) in breast milk, 3.1 μg/L (0.2–22.4 μg/L) in maternal urine, and 4.7 μg/L (0.3–134.5 μg/L) in infant urine; the median perchlorate concentration in breast milk was significantly higher than in maternal urine ($p < 0.01$). Median

Table 1. Subject Characteristics (n = 64)

Maternal age (years)	28.7 ± 7.9
Infant age (months)	1.6 ± 0.5
Ethnicity	
Caucasian	11%
Black	69%
Hispanic	9%
Asian	3%
Other/mixed	8%
Maternal birthplace	
U.S.	39%
Other	61%
Highest level of education	
Less than high school	13%
High school	56%
College	19%
Masters	9%
Higher than masters	3%
Marital status	
Single, never married	44%
Married	51%
Divorced	3%
Other	2%
Smoker	
Yes	6%
No	94%
Maternal multivitamin use	
Yes	77%
No	23%
Supplemental formula use per day	
None	35%
≥0–4 oz	24%
≥4 to 8 oz	25%
≥8–12 oz	8%
≥12–16 oz	5%
≥16 oz	3%

thiocyanate concentrations were 46.5 μg/L (2.9–1080 μg/L) in breast milk, 373.5 μg/L (31.1–2420 μg/L) in maternal urine, and 193 μg/L (21.7–1880 μg/L) in infant urine.

The results of the univariate correlation analyses are shown in Table 2. Breast milk iodine levels were positively correlated with maternal ($R = 0.35$, $p < 0.01$) and infant ($R = 0.56$, $p < 0.01$) urinary iodine concentrations and with breast milk perchlorate ($R = 0.26$, $p = 0.04$) and thiocyanate ($R = 0.51$, $p < 0.01$) levels. Breast milk perchlorate levels were positively correlated with maternal ($R = 0.45$, $p < 0.01$), but not infant, urinary perchlorate levels ($p = 0.55$). There were no significant correlations between breast milk and urinary thiocyanate concentrations of mothers ($p = 0.68$) or infants ($p = 0.45$). There were no significant correlations between infant TSH or FT4 and iodine, perchlorate, and thiocyanate levels in breast milk, maternal urine, and infant urine. In multivariable analyses, iodine, perchlorate, and thiocyanate levels in breast milk, maternal urine, and infant urine were not predictive of infant serum TSH ($p = 0.77$) or FT4 levels ($p = 0.12$) (Table 3).

Discussion

In the present report, we studied the relationships between environmental perchlorate and thiocyanate exposures, maternal and breastfed infant iodine nutrition, and infant serum thyroid function. Despite recent concerns about the potentially adverse effects of environmental perchlorate exposure on thyroid function, we found no associations between perchlorate levels in breast milk, maternal urine, and infant urine and infant serum thyroid function tests. We believe that these

Table 2. Correlations Between Breast milk and Urinary Iodine, Perchlorate, and Thiocyanate Levels and Infant Serum Thyroid Function

	Breast milk iodine	*Breast milk perchlorate*	*Breast milk thiocyanate*
Breast milk			
Perchlorate	$R = 0.26$, $p = 0.04$		
Thiocyanate	$R = 0.51$, $p < 0.01$		
Maternal urine			
Iodine	$R = 0.35$, $p < 0.01$	$R = 0.26$, $p = 0.04$	$R = 0.15$, $p = 0.24$
Perchlorate	$R = -0.11$, $p = 0.41$	$R = 0.45$, $p < 0.01$	$R = -0.05$, $p = 0.72$
Thiocyanate	$R = -0.27$, $p = 0.03$	$R = 0.11$, $p = 0.42$	$R = 0.05$, $p = 0.68$
Infant urine			
Iodine	$R = 0.56$, $p < 0.01$	$R = 0.02$, $p = 0.88$	$R = 0.21$, $p = 0.13$
Perchlorate	$R = 0.19$, $p = 0.17$	$R = -0.09$, $p = 0.55$	$R = 0.09$, $p = 0.55$
Thiocyanate	$R = 0.01$, $p = 0.93$	$R = 0.02$, $p = 0.91$	$R = 0.10$, $p = 0.45$
Infant serum TSH[a]	$R = 0.18$, $p = 0.19$	$R = -0.06$, $p = 0.67$	$R = 0.02$, $p = 0.87$
Infant serum FT4	$R = -0.01$, $p = 0.92$	$R = 0.06$, $p = 0.65$	$R = 0.13$, $p = 0.33$

[a]Log-transformed.
TSH, thyroid-stimulating hormone; FT4, free thyroxine.

Table 3. Multivariable Linear Regression Models Predicting Infant Serum Thyroid-Stimulating Hormone and Free Thyroxine Concentrations

	Parameter estimate	p
Dependent outcome: infant serum TSH (log-transformed) (model $p = 0.77$)		
Breastmilk perchlorate	−0.01	0.59
Breastmilk thiocyanate	−0.0004	0.40
Maternal urinary perchlorate	−0.03	0.57
Maternal urinary thiocyanate	0.00005	0.83
Infant urinary perchlorate	0.003	0.49
Infant urinary thiocyanate	−0.0001	0.77
Dependent outcome: infant serum FT4 (model $p = 0.12$)		
Breastmilk perchlorate	−0.007	0.61
Breastmilk thiocyanate	0.0004	0.11
Maternal urinary perchlorate	0.006	0.82
Maternal urinary thiocyanate	0.0002	0.05
Infant urinary perchlorate	0.004	0.12
Infant urinary thiocyanate	0.0001	0.39

data are reassuring and help clarify the current controversies surrounding the proposed regulation of the U.S. environmental perchlorate exposure.

The potential health risks of low-level environmental perchlorate and thiocyanate exposures are most relevant to women of childbearing age and their offspring, since insufficient maternal iodine during pregnancy and the immediate postpartum period results in various neurological and psychological deficits in children (12). Iodine deficiency has been associated with an increased risk of developmental delays, a decreased intelligence quotient (IQ) (13), and attention deficit and hyperactivity disorders (14). Infants born to mothers who received iodine during pregnancy have improved psychological and neurocognitive outcomes compared to those born to nonsupplemented mothers (15,16). However, a recent study has suggested that levo-T4 substitution in pregnant women with elevated serum TSH values did not affect cognitive function in their 3-year-old children, although the median gestational age of mothers was 12 weeks and 3 days, which may be too advanced during the gestational course to discern a measurable impact on neurocognitive outcomes (17).

Thyroid hormone is an important factor for oligodendrocyte differentiation and myelin distribution (18). Haddow *et al.* reported that the 7–9-year-old children of pregnant women with untreated hypothyroidism have an average of 7 IQ points lower than those of matched euthyroid control mothers (19). Low FT4 concentration in women during pregnancy is an independent predictor of impaired neurodevelopment in their children (20).

Iodine deficiency affects over 2.2 billion individuals (38% of the world's population) (21), and is the leading cause of preventable mental retardation worldwide (10). Population iodine sufficiency is defined by median urinary iodine concentrations $\geq 100\ \mu g/L$ in nonpregnant adults, lactating women, and children <2 years old (10). According to NHANES data, although the median urinary iodine concentration of the general population remained adequate at $\geq 100\ \mu g/L$ from the early 1970s to the early 1990s, there had been a decrease of >50% during this time period (22). Particularly concerning was the almost fourfold increase in the prevalence of urinary iodine values $<50\ \mu g/L$ among women of childbearing age, from 4% to 15%, over the two decades. Although the median urinary iodine concentration in U.S. pregnant women is $125\ \mu g/L$ according to the most recent (2005–2008) NHANES data, 35.3% have urinary iodine levels $<100\ \mu g/L$ (23). Thus, while the overall U.S. adult population remains iodine sufficient by WHO standards, a subset of pregnant and lactating women may have inadequate dietary iodine intake.

Sources of iodine in the U.S. diet have been difficult to identify due to its many potential sources, variation of iodine content in common foods, and lack of listed iodine amounts on food packaging. Also, urinary iodine concentration thresholds exist only for populations, but not for individuals, given significant day-to-day variation of iodine intake (24). As such, a public health approach to iodine supplementation in the United States has been advocated. The American Thyroid Association recommends that women in North America receive dietary supplements containing $150\ \mu g$ iodine daily during pregnancy and lactation and that all prenatal vitamins contain $150\ \mu g$ of iodine (25). Only 20.3% of pregnant and 14.5% of lactating women in the United States take a supplement containing iodine (26). Currently, 114 of 223 (51%) brands of prescription and nonprescription prenatal multivitamins marketed in the United States list iodine as a constituent, and many of those that do contain iodine do not contain the labeled amount, especially when kelp is the iodine source (27).

There has been a recent concern that low-level environmental perchlorate exposure has the potential to interfere with iodine utilization and thyroid function. Perchlorate appears to be ubiquitous and has been measured in the drinking water of communities around the United States, including Massachusetts (28). The U.S. Environmental Protection Agency (EPA) had previously placed perchlorate on its Candidate Contaminant List (29), and in February 2011, the EPA announced that the United States will proceed with regulating perchlorate in drinking water (30). This anticipated monitoring has previously been estimated to cost up to $140 million per year if an upper limit of 4 pg/L is targeted (31).

Perchlorate has been detected in foods such as lettuce, wheat, cows' milk (32), and in prenatal multivitamins. Infants and children have the highest estimated intakes of perchlorate by body weight (33), with urinary perchlorate levels <0.05–$25.8\ \mu g/L$ in 92 U.S. infants in a recent study (34). In the NHANES data from 2001–2002, perchlorate was detected in all 2820 spot urine samples (median urine perchlorate concentration $3.6\ \mu g/L$) (11) and was a significant negative predictor of total T4 and a positive predictor of TSH values in women, primarily those with urine iodine concentrations $<100\ \mu g/L$ (35). However, these relationships were not seen in men (35), among pregnant women in 3 Chilean cities (36,37), nor in a large European study assessing the serum thyroid function of iodine-deficient pregnant women (38). Cao and colleagues reported that infant urinary perchlorate and thiocyanate exposures were associated with both increased infant urinary TSH and T4 levels (39), an unanticipated finding, since increased TSH should be associated with lower T4. However, measurement of thyroid function in the urine is not standard, and the researchers found no significant associations between the two environmental agents and infant TSH and T4 levels when measured in serum (39).

Data regarding breast milk iodine and perchlorate concentrations in U.S. women are limited. Recent studies, among which 57 women were the largest sample, report a range of median breast milk iodine levels from 35–$155\ \mu g/L$ (8,32,40–42). We reported that the median breast milk iodine concentration in 57 Boston-area women was $155\ \mu g/L$ (8), similar to that of a 1984 study of 37 women ($178\ \mu g/L$), but higher than those (33.5, 37.9, 43.0, 55.2, and $71.3\ \mu g/L$) reported recently in four studies (32,40,41,43) and in the present report. Kirk *et al.* reported that breast milk iodide and perchlorate levels were inversely correlated in six samples with perchlorate concentrations of $\geq 10\ \mu g/L$, although there were no correlations between breast milk iodide and perchlorate in the full data set (32). We previously reported no correlation between breast milk and colostrum iodine and perchlorate concentrations, even in those breast milk samples with perchlorate concentrations $\geq 10\ \mu g/L$ (8,42). As was observed in our prior study (8), the present findings also demonstrate a significantly higher median perchlorate concentration in breast milk than in maternal urine, likely due to the ability of lactating breast cells to actively transport perchlorate into breast milk through the NIS (6).

The present study is the only study which has examined the potential effects of environmental perchlorate exposure on

serum thyroid function in breastfed infants. The recruited study population was underpowered to determine the statistical significance of perchlorate and thiocyanate exposures on serum infant thyroid function. However, perchlorate and thiocyanate levels in breast milk, maternal urine, and infant urine were associated with extremely small effect sizes on serum infant TSH and FT4 levels. Thus, we believe that environmental perchlorate and thiocyanate exposures are unlikely to be clinically relevant to the pituitary–thyroid axis, even in the subgroups of the general population who would be most vulnerable to their adverse effects.

We acknowledge some limitations to our study. The study sample, consisting of primarily Boston-area mothers and their infants of low socioeconomic status who were generally iodine sufficient, had overall adequate nutrition, and mostly nonsmokers, may not be representative of the general U.S. population. Our sample was also too small to obtain an estimate of the iodine sufficiency of the study population, which requires spot urinary iodine concentrations from a minimum for 125 individuals (44). Also, the iodine concentrations and potential perchlorate and thiocyanate levels of supplemental infant formula, that a majority of the mothers used, were not measured and accounted for. The temporal relationship between the iodine content in breast milk and recent dietary iodine intake is unknown, and it is unclear if a random breast milk iodine concentration is an accurate indication of the dietary iodine available to breastfed infants. However, our findings do represent the largest sample size of breast milk iodine, perchlorate, and thiocyanate levels and infants' serum thyroid function in the United States and provide further understanding on the relationship of breast milk iodine content and infant urinary iodine concentrations.

We conclude that the mothers and their breastfed infants in our study sample were generally iodine-sufficient. Although environmental perchlorate and thiocyanate are ubiquitous, our results do not support the concern that maternal and infant perchlorate and thiocyanate exposures in low levels affect infant serum thyroid function.

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Disclosure Statement

The authors declare that no competing financial interests exist.

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