HYPOPHYSAL HORMONE, REQUIRING adequate iodine intake, is critical for neurodevelopment in utero and in early life. Worldwide, iodine deficiency remains the leading cause of preventable mental retardation (1). Since the 1920s, U.S. dietary iodine has generally been adequate. However, among U.S. women of childbearing age (15–44 yr), median urinary iodine levels, a biomarker for dietary iodine, decreased by over 50% from 1971–1994 according to data from the National Health and Nutrition Examination Survey; NIS, sodium/iodide symporter.

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Abbreviations: NHANES, National Health and Nutrition Examination Survey; NIS, sodium/iodide symporter.

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smoke contains significant levels of cyanide that is metabolized to thiocyanate, a known competitive inhibitor of the NIS. Elevated serum thiocyanate levels may inhibit NIS-mediated transport of iodide in the lactating breast, leading to reduced breast milk iodine levels.

The objective of the present study was to determine whether breast milk iodine concentrations in Boston-area women are adequate for infant nutrition and whether breast milk iodine concentrations may be associated with environmental perchlorate or cigarette smoke exposure. Levels of iodine and perchlorate in breast milk were compared with those measured in 17 brands of infant formulae.

Subjects and Methods

We obtained breast milk and urine samples from 57 healthy Boston-area volunteers (range, 19–45 yr; mean age, 30 ± 6 yr), at 10–250 (median, 48) days postpartum, between July 2002 and April 2006. The local Institutional Review Board approved the protocol, and informed consent was obtained from all participants. Volunteers were recruited through various means, including a community-based new mothers' group, routine postpartum visits at a hospital-based inner-city obstetric clinic, and flyers posted in a hospital lobby. Of the women studied, 72% reported taking prenatal multivitamins, but only three were using iodine-containing multivitamin preparations.

Twenty-seven women completed a questionnaire regarding their demographics and intake of dietary iodine and iodine-containing multivitamins. Spot urinary iodine measurements were obtained from all subjects. Urine perchlorate, creatinine, and cotinine (a metabolite of nicotine in cigarette smoke) concentrations were also measured. Samples of breast milk (approximately 10 ml) were collected at the start of a feed using either hand expression or a breast pump in 27 of the women. Samples of breast milk were collected in 5-ml increments sequentially, using a breast pump in the other 30 women. In this subset of 30 subjects, we measured breast milk iodine concentrations both at the start of a feed and sequentially throughout a single feed to assess any potential intrafeed variation. In the women whose breast milk was collected in sequential increments, the mean breast milk iodine concentration is reported. Enough breast milk was available in 49 (86%) and enough urine was available in 56 (98%) of the samples for the measurement of perchlorate. Enough urine was available in 56 (98%) of the samples for the measurement of cotinine. All breast milk and urine samples were obtained within the same hour.

Seventeen brands of infant formulae were also assessed for iodine and perchlorate levels. A single sample of each different type of liquid formula milk available at a supermarket in the Boston area was purchased for testing. Thirteen of these brands were sold in concentrated form and designed to be diluted by half before use. Iodine and perchlorate levels were measured directly in these samples, and the results were divided by half to reflect the concentration intended for infant use. The other eight brands were sold ready for use.

Breast milk, infant formulae, and urine iodine concentrations were measured spectrophotometrically by a modification of the method of Benotti et al. (16). Iodine concentrations were measured at least twice; in 95% of the samples, the initial two measurements were within 15% of each other, and the two values were averaged. In the case where the initial two measurements were not within 15% of each other, a third measurement was obtained, and the average of all measurements was reported. Cotinine measurements were performed by immunoassay (Immulite 2000 Nicotine Metabolite Assay; Diagnostic Products Corp., Los Angeles, CA). Urine creatinine measurements were performed using Jaffe’s alkaline picrate method. The perchlorate content of breast milk, infant formulae, and urine samples was measured at the Centers for Disease Control and Prevention laboratories in Atlanta, GA, using ion chromatography-mass spectrometry (17). All statistical analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC). Spearman's rank correlation coefficient was used to determine whether linear associations were present, and multivariate linear regression was used to determine significant predictors of breast milk iodine concentration. Intrafeed variation in the iodine content of the subjects whose breast milk was measured sequentially was assessed using repeated-measures ANOVA. Differences in breast milk and urine iodine values between smokers and nonsmokers and differences in measured and labeled infant formula iodine content were assessed using an independent t test. Differences in mean values across subject groups were assessed by ANOVA. Differences in median iodine and perchlorate values in breast milk compared with infant formula were assessed using the Wilcoxon rank sum test.

Results

Median iodine content in the 57 breast milk samples was 155 μg/liter [range, 2.7–1968 μg/liter; mean (± sd), 205 ± 271 μg/liter]. There was no significant intrafeed variation in the iodine content of the subjects whose breast milk was assessed sequentially during a single feed. Breast milk iodine concentrations in the three women who reported using iodine-containing multivitamins were 28, 68, and 187 μg/liter. In a subset of 27 women whose use of iodized table salt was determined, there was no significant difference in breast milk iodine levels between the subjects who reported regular, occasional, or no use of iodized salt (P = 0.16). There was a slight but significant positive correlation between breast milk iodine content and maternal age (r² = 0.08; P = 0.04) but not infant age (P = 0.4). Median urine iodine content was 114 μg/liter (range, 25–920 μg/liter; mean, 155 ± 142).

Perchlorate was detectable in all 49 breast milk samples (median, 9.1 μg/liter; range, 1.3–411; mean, 33 ± 77) and 56 urine samples tested (median, 3.0 μg/liter; range, 0.37–127; mean, 8.2 ± 19). Cotinine was detected in the urine of 32 (57%) of 56 urine samples tested (range, 1.5–1575 ng/ml), with six (19%) of these likely to be smokers (urinary cotinine > 500 ng/ml). Mean breast milk iodine was 62 ± 35 μg/liter in the smokers and 221 ± 285 μg/liter in the nonsmokers (P = 0.0005), whereas urinary iodine did not differ between these groups (P = 1.0). There were significant differences in the mean breast milk perchlorate concentrations between the women recruited from the mothers seen at routine postpartum visits at a hospital-based inner-city obstetric clinic (n = 10; 88.0 ± 150.0 μg/liter), those from the community-based new mothers’ group (n = 9; 50.0 ± 62.5 μg/liter), and those recruited by the hospital postings (n = 30; 10.3 ± 13.8 μg/liter) (P for difference across the three groups was 0.01). There were no significant differences between breast milk iodine, urinary iodine, urinary perchlorate, and urinary cotinine across these subject groups.

Breast milk and urine iodine content in micrograms per liter were not significantly correlated (r² = 0.06; P = 0.08). A significant positive correlation between breast milk iodine and urine iodine content per gram creatinine was observed (r² = 0.27; P < 0.0001). There was a significant positive correlation between breast milk perchlorate and urine perchlorate concentrations (r² = 0.11; P = 0.02). There were no significant correlations between breast milk iodine and perchlorate concentrations (n = 49; r² = 0.05; P = 0.1) (Fig. 1), including the 23 women whose breast milk perchlorate values were 10 μg/liter or higher (r² = 0.002; P = 0.8). Breast milk iodine and urine perchlorate concentrations (r² = 0.004; P = 0.7) were not significantly correlated. There was a slight but significant inverse correlation between breast milk iodine and urine cotinine concentrations (r² = 0.13; P = 0.006) (Fig. 2). In multivariate models, breast milk perchlorate (P = 0.9), urine perchlorate (P = 0.4), urine cotinine (P = 0.2), and baby
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Fig. 1. Correlation between breast milk iodine and perchlorate concentrations.

Fig. 2. Correlation between breast milk iodine and urine cotinine concentrations.

Fig. 3. Mean breast milk iodine content by quartile, with SD shown numerically. Dotted line corresponds to approximate breast milk iodine content required to achieve adequate intake (110–130 μg/liter) for an infant age 0–6 months.

Iodine is avidly concentrated in the lactating breast, due to increased expression of NIS during lactation (18). Breast milk iodine levels are highest in transitional milk (2–5 d postpartum) and decrease to stable levels by 10 d postpartum (18). We report that among the 30 subjects whose breast milk was sampled sequentially, there were no significant intrafeed variations in iodine concentration. A recent study suggests, however, that there is a substantial amount of day-to-day and diurnal variation in breast milk iodine excretion (19).

The median breast milk iodide level in a 1984 sample of 37 U.S. women was 178 μg/liter (20), which is similar to the median iodine value of 155 μg/liter observed in our study. However, the median breast milk iodine concentration observed in our study was also far higher than the mean value of 38.5 μg/liter reported in 55 Chilean women (21); the iodine content of breast milk from the Chilean women was measured by the same method as reported in the current manuscript (16). Tellez et al. (21) in the Chilean study and Chan et al. (22) in an Australian study reported that breast milk iodine levels correlate with urinary iodine per gram creatinine but not with unadjusted urinary iodine values, as seen in the present study.

Assuming breast milk intake of 0.78 liter/d (6) as the only source of breastfed infant iodine nutrition, and that single samples are representative of daily breast milk iodine content, which may not be correct due to the day-to-day and diurnal variation in breast milk iodine content noted by Kirk et al. (19), 47% of women sampled may have been providing breast milk with insufficient iodine to meet infants’ daily requirements. The difference between median breast milk and measured infant formula iodine levels was not signifi-
The question of whether low-level environmental perchlorate exposure has clinical consequences has been extremely controversial (24) and has been the topic of a recent National Academy of Sciences review (7). Median urine perchlorate levels in the current study were 3.6 μg/liter in 2820 spot urine specimens in the lowest quintile. This is higher than the levels reported by Kirk et al. (14, 19) in two recent studies (medians, 3.3 and 4.0 μg/liter) and in the infant formulae currently measured (median, 1.50 μg/liter). There was a significant difference in the perchlorate levels among the subjects when grouped by method of recruitment, which may be attributable to the relatively small sample size as well as the demographic differences of the study population. In data from NHANES 2001–2002, non-Hispanic Whites had lower levels of urinary perchlorate than non-Hispanic Blacks (13). Perchlorate was also detectable in all 56 human urine samples tested, with median levels (2.90 μg/liter) consistent with previously published data (17). The source of this perchlorate exposure is unknown and merits further investigation.

Kirk et al. (14) previously speculated that milk perchlorate of 10 μg/liter or higher may lead to reduced milk iodide levels. Despite the fact that 47% of our samples contained perchlorate at concentrations of at least 10 μg/liter, we found no correlation between milk perchlorate and milk iodine content. Our results are consistent with the results of Lengemann (26), who found dairy cattle milk iodine excretion unaffected by perchlorate doses less than 0.1 mg/kgd. A recent study of pregnant and lactating Chilean women consuming tap water known to contain naturally occurring perchlorate (~110 μg/liter) also found no correlation between perchlorate exposure and breast milk iodine or newborn thyroid function tests (21). One possible reason for the lack of correlation in these studies might be the diurnal and day-to-day variation in breast milk concentrations of both iodine and perchlorate (19).

Thiocyanate, as a metabolite of cigarette smoking, is also a known inhibitor of the NIS. Laurberg et al. (15) reported that although both smokers and nonsmokers had stable levels of urinary iodine postpartum, smokers (defined as those with urinary cotinine >500 ng/ml) had lower concentrations of breast milk iodine, and their infants had lower concentrations of urinary iodine. Similarly, we found a small but significant difference in the perchlorate levels among the subjects when grouped by method of recruitment, which may be attributable to the relatively small sample size as well as the demographic differences of the study population. In data from NHANES 2001–2002, non-Hispanic Whites had lower levels of urinary perchlorate than non-Hispanic Blacks (13). Perchlorate was also detectable in all 56 human urine samples tested, with median levels (2.90 μg/liter) and concentrations of urinary iodine. Similarly, we found a small but

<table>
<thead>
<tr>
<th>Milk-based</th>
<th>Labeled iodine (μg/liter)</th>
<th>Measured iodine (μg/liter)</th>
<th>Measured perchlorate (μg/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfamil A.R. Lipil (thickened with rice starch, iron-fortified)</td>
<td>67</td>
<td>224</td>
<td>4.1</td>
</tr>
<tr>
<td>Enfamil LactoFree Lipil (lactose-free, iron-fortified)</td>
<td>100</td>
<td>120</td>
<td>0.4</td>
</tr>
<tr>
<td>Enfamil Lipol Low Iron</td>
<td>67</td>
<td>158</td>
<td>2.1</td>
</tr>
<tr>
<td>Enfamil Lipol (infant formula)</td>
<td>102</td>
<td>172</td>
<td>1.7</td>
</tr>
<tr>
<td>Enfamil with Iron (milk-based)</td>
<td>67</td>
<td>102</td>
<td>2.0</td>
</tr>
<tr>
<td>Nestle Good Start with Iron (Supreme, with easy to digest Comfort Proteins)</td>
<td>80</td>
<td>145</td>
<td>0.3</td>
</tr>
<tr>
<td>Nestle Good Start with Iron (Supreme, with easy to digest Comfort Proteins)</td>
<td>80</td>
<td>178</td>
<td>0.2</td>
</tr>
<tr>
<td>Nutramigen Lipil (lactose-free, hypoallergenic, iron-fortified)</td>
<td>100</td>
<td>193</td>
<td>1.5</td>
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<tr>
<td>Similac Advanced Infant Formula with Iron</td>
<td>40</td>
<td>122</td>
<td>1.5</td>
</tr>
<tr>
<td>Similac Alimentum Advance with Iron (protein hydrolysate formula with iron, hypoallergenic)</td>
<td>100</td>
<td>158</td>
<td>2.0</td>
</tr>
<tr>
<td>Similac Infant Formula Low Iron</td>
<td>40</td>
<td>153</td>
<td>2.1</td>
</tr>
<tr>
<td>Similac Infant Formula with Iron</td>
<td>40</td>
<td>142</td>
<td>1.6</td>
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<td>Similac Lactose Free Infant Formula with Iron</td>
<td>60</td>
<td>143</td>
<td>1.4</td>
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<tr>
<td>Similac Neosure Advance with Iron</td>
<td>100</td>
<td>178</td>
<td>2.5</td>
</tr>
<tr>
<td>Soy-based</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Enfamil Prosobee Lipil (milk-free, lactose-free, iron-fortified)</td>
<td>100</td>
<td>112</td>
<td>0.3</td>
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<tr>
<td>Enfamil Prosobee Soy Infant Formula (milk-free, lactose-free, iron-fortified)</td>
<td>100</td>
<td>122</td>
<td>0.6</td>
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<tr>
<td>Similac Isomil Soy Formula with Iron (milk-free, lactose-free)</td>
<td>100</td>
<td>84</td>
<td>0.4</td>
</tr>
</tbody>
</table>

All of the iodine and perchlorate levels reported here reflect the concentration intended for infant use.

a The nine brands of infant formula that were sold in concentrated form and designed to be diluted by half before use.

b All of the iodine and perchlorate levels reported here reflect the concentration intended for infant use. The nine brands of infant formula that were sold in concentrated form and designed to be diluted by half before use.
significant inverse correlation between breast milk iodine and urine cotinine concentrations and found that smokers had significantly lower breast milk iodine levels than nonsmokers. Breastfeeding women should clearly be counseled against smoking for this and many other reasons.

We believe that a larger study of breast milk iodine content and its relationship to perchlorate exposure and maternal iodine nutrition is warranted in U.S. women. Although in the present study we found no correlation between breast milk iodine and perchlorate concentrations, the relatively low levels of iodine and relatively high levels of perchlorate in human milk do raise concerns. One limitation of the study was that we do not know the impact of breast milk perchlorate on the thyroidal iodine uptake and thyroid function of the breastfed infants. The American Thyroid Association has recently identified as a research priority the measurement of breast milk iodine levels in U.S. women and correlation with maternal iodine nutrition and factors such as smoking (27). Very few women in the present study reported routine use of an iodine-containing multivitamin. We feel that there should be more public awareness of the importance of dietary iodine in lactation and that iodine (at least 150 µg) should be included in standard prenatal multivitamins consistent with the recent recommendations of the National Academy of Sciences (7) and the American Thyroid Association (8). It is important to note that epidemiological studies consistently point to the value of human milk as the healthiest food for infants. Thus, the benefits of human milk outweigh possible effects of environmental toxicants present.

Acknowledgments

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The role of the Centers for Disease Control (CDC) in this study dealt exclusively with perchlorate exposure assessment. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of CDC.

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