Published in final edited form as:
Environ Sci Technol. 2011 May 1; 45(9): 4127–4132. doi:10.1021/es103160j.

Perchlorate exposure and dose estimates in infants

Liza Valentín-Blasini[†], **Benjamin C. Blount**[†,*], **Samaret Otero-Santos**[†], **Yang Cao**[‡], **Judy C. Bernbaum**[§], and **Walter J. Rogan**[¶]

[†] Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30341, USA

[‡] Department of Health Statistics, Faculty of Health Services, Second Military Medical University, Shanghai, China

[§] Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

[¶] Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA

Abstract

Perchlorate is a naturally occurring inorganic anion used as a component of solid rocket fuel, explosives, and pyrotechnics. Sufficiently high perchlorate intakes can modify thyroid function by competitively inhibiting iodide uptake in adults; however little is known about perchlorate exposure and health effects in infants. Food intake models predict that infants have higher perchlorate exposure doses than adults. For this reason, we measured perchlorate and related anions (nitrate, thiocyanate, and iodide) in 206 urine samples from 92 infants ages 1–377 days and calculated perchlorate intake dose for this population of infants. The median estimated exposure dose for this population of infants was 0.160 μg/kg/day. Of the 205 individual dose estimates, 9% exceeded the reference dose of 0.7 μg/kg/day; 6% of infants providing multiple samples had multiple perchlorate dose estimates above the reference dose. Estimated exposure dose differed by feeding method: breast-fed infants had a higher perchlorate exposure dose (geometric mean 0.220 μg/kg/day) than infants consuming cow milk-based formula (geometric mean 0.103 μg/kg/day, $p<0.0001$) or soy-based formula (geometric mean 0.027 μg/kg/day, $p<0.0001$), consistent with dose estimates based on dietary intake data. The ability of perchlorate to block adequate iodide uptake by the thyroid may have been reduced by the iodine-sufficient status of the infants studied (median urinary iodide 125 μg/L). Further research is needed to see whether these perchlorate intake doses lead to any health effects.

Introduction

Perchlorate is an inorganic anion used in solid rocket fuel, explosives, and pyrotechnics (1). It forms naturally in the atmosphere and accumulates in arid regions (2, 3). Perchlorate is widespread in the environment, resulting in human exposure. Such exposure is a health concern because sufficiently high doses are known to impair thyroid function by

[*]Corresponding author phone: 770-488-7894; BBlount@cdc.gov.

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

Supporting Information Available

Supporting Information includes a brief description of the study enrollment criteria, analytical precision of the method (Table S1), multivariate correlation coefficients (Table S2) and detailed distribution of perchlorate doses (Table S3). This material is available free of charge at http://pubs.acs.org.

competitively inhibiting iodide uptake (4, 5). Whether the doses that result from environmental exposure affect thyroid function is an area of active research. In data from the 3rd National Health and Nutrition Examination Survey, women with higher urinary perchlorate and urinary iodine less than 100 μg/L had higher serum thyroid stimulating hormone (TSH) and lower thyroxine (T4) (6). In a report from our group, infants with higher urinary perchlorate and thiocyanate, and urinary iodide less than 100 μg/L had higher urinary TSH and T4 (7). Given the potential for widespread exposure to iodide uptake inhibitors (perchlorate, thiocyanate, and nitrate), characterizing the doses at which thyroid associations are observed is important, especially for children. Perchlorate exposure in the United States (8) is generally at doses less than the U.S. Environmental Protection Agency (EPA) reference dose (RfD) of 0.7 μg/kg/day. The RfD is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (9). Data from the National Health and Nutrition Examination Survey indicate that perchlorate exposure doses were highest in the youngest age group surveyed (6–11 yrs), perhaps because food consumption per kg body weight is higher at younger ages. Dose estimates from perchlorate levels in breast milk, infant formula, and tap water indicate that infants are likely to have higher perchlorate intakes per body weight than adults, with exposure doses possibly exceeding the RfD (10, 11–13). These estimates are in agreement with the U. S. Food and Drug Administration Total Diet Survey study reporting the highest estimated intakes on a body weight basis in this age group. (14).

The National Research Council suggested that pregnant women, fetuses, and infants are the life stages with the greatest potential sensitivity to perchlorate (15). Neonates are a particularly sensitive life stage because they cannot rely on maternal thyroid hormone. Therefore, the neonate must synthesize its own thyroid hormones (T4 and 3, 5, 3′-triiodothyronine (T3)) to maintain normal growth and development. Thyroid hormones synthesis depends, in part, on an adequate supply of iodide in the thyroid. The sodium-iodide symporter (NIS) is a transmembrane protein that pumps iodide into the thyroid; it can also actively transport perchlorate across membrane barriers in other NIS-containing tissues like the lactating mammary gland (16). Exposure to perchlorate and other NIS inhibitors (e.g. nitrate and thiocyanate) among lactating women could competitively inhibit iodide secretion into milk and decrease iodide intake by the infant (12). Consistent with these concerns, exposure to perchlorate and thiocyanate has been associated with increased urinary TSH and T4 in infants (7).

Although infants may be more sensitive to perchlorate and have higher exposure doses than adults, we are not aware of reports of directly measured perchlorate in infant urine. In this study, we measured perchlorate, nitrate, thiocyanate and iodide in 206 urine samples collected from 92 infants, ranging in age from 1 to 377 days. By measuring these four toxicologically-related anions we improve exposure assessment of this sensitive life stage, and thus improve the interpretation of any potential thyroid effect resulting from NIS inhibitor exposure (7).

Material and Methods

Study Description

We used data and urine specimen collected as part of the Study of Estrogen Activity and Development (SEAD). We analyzed a subset of 206 urine samples collected either by using a cloth diaper or urine bag from 92 infants exclusively consuming either breast milk, cow milk-based formula or soy-based formula. A detailed description of this cross-sectional, semi-longitudinal study has been published elsewhere (7, 17).

Laboratory Methods

We quantified perchlorate, iodide, nitrate, and thiocyanate in urine by isotope dilution and ion chromatography/tandem mass spectroscopy (IC-MS/MS), as reported previously (18). Each batch of unknown urine samples was bracketed by aliquots of quality control materials and blank samples for the purpose of assessing method accuracy, precision, and contamination (See online supporting information, Table S1). Reported results met the accuracy and precision specifications of the quality control/quality assurance program of the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (19). Urinary creatinine concentrations were determined using an automated colorimetric method on a Roche/Hitachi Modular Analytics SWA system (Roche Diagnostics Corp., IN, USA).

Blank Analysis and Perchlorate Corrections

Lot-matched diaper material (n = 9) was tested for analytes by the addition of 10 mL of deionized water to diaper material. The wet areas of diaper were cut out with scissors and transferred to a syringe barrel; fluid was forced from the sample by compression. The resulting fluid was analyzed as described for the urine samples. The blank diaper samples contained no measurable iodide, nitrate, or thiocyanate; however, the diapers did contain measurable perchlorate (1.24 ± 0.23 μg/L). Therefore, perchlorate concentrations of diaper-press urine samples were adjusted by subtracting 1.24 μg/L.

Statistical Methods and Data Analysis

We conducted statistical analysis using SAS, version 9.0 (SAS Institute Inc., Cary, NC) and JMP, version 8.0 (SAS Institute Inc., Cary, NC). Univariate analysis indicated that all analytes were log-normally distributed. For statistical purposes, all samples with concentrations below the lowest reportable level were replaced with an imputed value (LOD/v2). The LODs for perchlorate, nitrate, thiocyanate, and iodide were 0.05 μg/L, 500 μg/L, 10.0 μg/L, and 0.33 μg/L, respectively. The LOD was based on calculating the standard deviation at zero concentration (S_0), as described by Taylor (20).

Dose Estimation Methods

We estimated daily perchlorate dose on the basis of measured spot urine perchlorate, urine creatinine, infant weight, and estimated daily creatinine excretion rate (mg/day), according to recently published methods (21). Daily creatinine excretion (CE) was calculated by use of the following equations:

$$\text{CE g/day} = (36 + 10.33\,(\text{age in months})) \div 1000 \quad \text{for age} < 3 \text{ months}$$
$$\text{CE g/day} = (67 + 5.47\,(\text{age in months} - 3)) \div 1000 \quad \text{for age} > 3 \text{ months and} < 13 \text{ months}$$

Daily perchlorate dose was then estimated by use of the following formula:

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

Results and Discussion

Differences in diet between adults and infants predict that infants would have higher perchlorate intake doses than adults (11). Pharmacological doses of perchlorate can reduce thyroid hormone production by competing with iodide for uptake by NIS (5). Therefore, perchlorate toxicity may be modulated by iodide. For this reason, in addition to measuring perchlorate, nitrate and thiocyanate we also quantified iodide in the infant urine samples.

The World Health Organization (WHO) defines iodine sufficiency for populations of children less than 2 years old as a median urinary iodine concentration ≥100 μg/L (22). In this study, we measured iodide (not total iodine), the predominantly occurring and biologically available form of iodine (15). Thus the group of infants we studied was iodine-sufficient based on a median iodide concentration of 125 μg/L. Median urinary iodide levels in these infants agree well with published studies of European infants with population medians ranging from 92–162 μg/L (23–25).

Our study enrolled infants who met relatively stringent criteria for inclusion into feeding categories of breast milk, cow milk-based formula, or soy-based formula, so that we could compare perchlorate exposure by feeding method. Table 1 describes a more detailed distribution of urinary concentrations of perchlorate, nitrate, thiocyanate, iodide and creatinine categorized by feeding method than presented by Cao et al (7) Additionally, we present the results in concentration units because urinary creatinine excretion rates differ between breastfed and formula-fed infants (26), and thus differences in creatinine-adjusted toxicant levels between different feeding groups would be influenced both by exposure and creatinine levels. Consistent with previously reported results (26), we found that urine creatinine excretion was associated with the type of feeding, with breast fed infants (mean 12.99 mg/dL) excreting significantly less ($p=0.03$) creatinine than formula fed infants (mean 18.50 mg/dL). The proportion of detection for perchlorate was highest in breast-fed infants (95%), followed by infants consuming cow milk-based formula (86%) and infants consuming soy formula (68%). Breast-fed infants had significantly higher urinary perchlorate levels than infants who consumed cow milk-based formula ($p=0.004$) and soy formula ($p<0.001$) consistent with the findings of others (12, 13, 27, 28). Within the formula-fed infants, consumption of cow milk-based formula led to higher urinary perchlorate levels than did consumption of soy-based infant formula ($p<0.001$). A similar pattern was observed for thiocyanate: breast-fed ($p<0.001$) and cow milk-based formula ($p=0.006$) groups had significantly higher urinary thiocyanate levels than did the soy formula-fed group. The opposite was true for urinary nitrate levels: infants consuming cow milk-based formula ($p=0.017$) or soy formula ($p=0.005$) had significantly higher levels of urinary nitrate than the breast-fed group. Future measurement of nitrate levels in breast milk, infant formula, and water used to prepare infant formula may offer an explanation for this observation

The urinary iodide levels observed among the different feeding groups are consistent with the published iodide and iodine levels in breast milk and infant formula (12, 13, 27, 29). Infants consuming cow milk-based formula had significantly higher urinary iodide levels ($p=0.003$) than infants consuming soy formula. Previous analysis of different brands of infant formula found that soy formulas (N=9) contained average iodide concentration of (88 μg/L), about 40% lower than average iodide concentrations in cow milk-based formula (154 μg/L, N=15). Thus the relatively lower levels of iodide in soy-based infant formula lead to relatively lower urine iodide levels in infants consuming soy formula compared with cow milk-based formula.

We evaluated the correlation between the different analytes in urine. Perchlorate and iodide levels were positively correlated ($r=0.55$) in urine samples, while levels of the other anions showed no significant relation (See online supporting information, Table S2). The positive correlation of perchlorate and iodide was found in both breast-fed and formula-fed infants, likely resulting from positively correlated levels of these two anions in breast milk and infant formula. One explanation is that the same food crop processes that concentrate perchlorate (e.g. water evaporation in edible leaves) may also concentrate iodine. The positive correlation of perchlorate and iodide in infant urine samples provides some evidence that perchlorate was not out-competing iodide for transport during lactation for the

maternal/infant pairs in this study. Alternatively, the much higher levels of iodide in the infants could have masked a subtle perchlorate effect. Further research is needed to better characterize the potential of perchlorate to inhibit iodide transport from lactating woman to breastfed infant (13).

Because some infants had up to four visits during the study and thus had up to four urine samples analyzed, we used a mixed linear model that accounted for correlations among multiple measurements from the same subject. Candidates for covariates used in the model were age, BMI, feeding method, and sex. Low intra-individual correlation coefficients (ICCs) were observed for these infants for perchlorate, perchlorate dose, nitrate and creatinine (rho=0.07, 0.12, 0.02 and 0.28, respectively). Compared with these analytes, thiocyanate showed higher intraclass correlation (rho=0.40), possibly because of its longer physiological half life (~ 6 days) compared with the other analytes (~8 hrs). Iodide had the highest ICC (rho=0.95) of analytes measured, possibly indicative of consistent fortification of formula with iodine and/or consistent iodine intake and secretion by the lactating mothers of the infants. Some of the variability observed could be due to differences in the timing of urine collection related to feeding among the different visits, or in the amount of diaper contamination. Alternatively, the exposure may have changed between different sampling periods. Breast milk perchlorate levels can vary significantly over a single day (12) likely because of varied and episodic perchlorate intake from diet that will vary even more widely as maternal diet changes across seasons. Additionally, while perchlorate levels in infant formula are likely to vary less than those in breast milk, infants may have consumed different brands and volumes at different sampling times. A recent evaluation of perchlorate levels in infant formula found significant variability among formula manufacturers (121%), types (64%), and among different lots of the same product from the same manufacturer (32%) (28). Another potential source of variability is the hydration state of the infant, which can be accounted for by dividing urinary perchlorate by urinary creatinine. Infants older than six months also could have varied and episodic perchlorate exposure from intake of different “solid” foods containing differing amounts of perchlorate (14). Finally, variability in dose estimates would have been reduced by collecting 24 hr urine instead of spot samples, but 24 hr urine collection is impractical for infants. Based on all these sources of variability, we conclude that the study would have been strengthened by collecting multiple urine samples for each time period, and collecting further information on the complete dietary habits of the infants and breast feeding women.

The National Academy of Sciences (NAS) recently evaluated the health implications of perchlorate ingestion and suggested a perchlorate reference dose (0.7 μg/kg/day) that the EPA subsequently adopted (30). The reference dose estimates an oral intake that is likely to be without an appreciable risk of deleterious effects during a lifetime. The NAS specified iodine-deficient pregnant women, fetuses and neonates as the life stages most sensitive to potential adverse health effects from perchlorate exposure. To provide toxicological perspective on our data, we estimated perchlorate dose on the basis of measured spot urine perchlorate and creatinine (21). The equations used to calculate intake dose were based on children consuming cow’s milk or modified cow’s milk (21, 31–33). Therefore these dose estimation equations are only valid for infants with a similar relation of age and creatinine excretion. Both our data and a previous report (26) find that breast-fed infants excrete significantly less creatinine than formula fed infants of the same age. Thus creatinine excretion estimates for breastfed infants must be adjusted accordingly to account for lower creatinine excretion rates compared with formula-fed infants. Therefore we adjusted the estimated perchlorate dose for breast-fed infants by multiplying by 0.69 to account for reduced 24 hr creatinine excretion in breast-fed infants relative to formula fed infants. The 0.69 correction factor was calculated based on the ratio of the geometrical means of creatinine levels in urine samples collected from breastfed infants compared with formula-

fed infants. Further research is needed to better characterize differences in creatinine excretion in infants and thus improve estimates of toxicant intake doses in this susceptible population.

Distribution of estimated perchlorate exposure doses in 205 urine samples from the infants we studied are presented in Table 2. A more detailed distribution of perchlorate doses is presented in the online supporting information, Table S3. Estimation of perchlorate dose in these infants revealed a median of 0.160 μg/kg/day, well below the EPA reference dose of 0.7 μg/kg/day. The median estimated perchlorate dose for infants is 2.4 times higher than the median dose estimated for adults in the U.S. population [0.066 μg/kg/day] (8). The higher perchlorate doses estimated for infants, compared to adults, is likely due to higher consumption of perchlorate-containing foods and liquids per kilogram body weight. On the basis of perchlorate levels in breast milk and infant formula, previous reports have estimated that some infants may have perchlorate doses that exceed the RfD (10–13). Our dose estimates, which are based on measured body weight and urinary levels of perchlorate and creatinine, find the central tendency of dose estimates to be below the RfD while some of the highest doses exceed the RfD. Of the 205 spot urine dose estimates, 9% exceeded the reference dose of 0.7 μg/kg/day; 6% of infants providing multiple samples had multiple perchlorate dose estimates above the reference dose. The infants with perchlorate dose estimates > RfD on more than one occasion are of more concern, given that perchlorate inhibition of iodide uptake would need to be chronic to result in thyroid inhibition (4, 15). No estimated doses exceeded the no effect level (7 μg/kg/day) calculated by Greer et al (4) based on a 14 day study of controlled perchlorate intake (7 – 500 μg/kg/day) by healthy adults. The reference dose was derived by dividing the Greer et al (4) no effect level by an uncertainty factor of 10 so that the reference dose would “protect sensitive populations and life stages” (15). However sensitive life stages such as infants were not included in the Greer et al study (4). Therefore the actual perchlorate dose that might cause a health effect in infants is not known. With the current study we confirm the prediction that infants are likely to intake higher perchlorate doses compared with adults (10). Furthermore, these exposures to perchlorate and thiocyanate are associated with increased TSH and T4 levels in infant urine (7). Further research is needed to clarify the health impact of perchlorate exposure in infants.

The magnitude of perchlorate dose was associated with the feeding method, with breast-fed infants having 18 of the 20 highest perchlorate doses. Estimated perchlorate doses for breast-fed infants were significantly higher than the doses of infants consuming cow milk-based formula ($p<0.001$), and infants consuming cow milk-based formula had significantly higher estimated doses than did soy formula-fed infants ($p<0.001$). These estimates are consistent with most food intake model predictions (10, 12–14). The one exception was that our estimated perchlorate doses for breast-fed infants (mean 0.420 μg/kg/day), were significantly lower ($p<0.0001$) than perchlorate dose estimates (mean 1.1 μg/kg/day) based on pooled breast milk samples collected from 13 lactating women in a previously published study (13). Small studies such as this may be biased due to diet, geography and other variables that can significantly impact perchlorate intake. Further research is needed to better quantify infant exposure to perchlorate and other NIS inhibitors.

We also examined the influence of age on estimated perchlorate dose. While only 27% of the 205 samples were collected from infants less than two months of age, 11 of the 20 highest estimated perchlorate doses were from urine collected from infants ≤ 2 months of age. These findings agree well with previously published predictions that infants would be exposed to higher perchlorate doses during their first 2 months of life (12). Declining perchlorate dose following the first two months of infancy is likely due to the declining ratio of milk intake per unit body weight as infants age (34). We also compared our data with

perchlorate exposure dose estimates for ages 6–11 months from the U.S. Food and Drug Administration Total Diet Study. On the basis of analysis of perchlorate in infant food and consumption data, the Total Diet Study estimated that U. S. infants of ages 6–11 months had a mean dietary perchlorate dose of 0.26–0.29 μg/kg/day (14). Our perchlorate dose estimates for this same age group (mean, 0.208 μg/kg/day) agreed well with the FDA estimated doses. The close agreement of our convenience population data with the nationally representative FDA dose estimates supports the ability to generalize our findings.

Our finding of higher perchlorate exposure in breast-fed infants should not discourage women from breast feeding. Although perchlorate and other environmental chemicals in human milk leads to infant exposure through breastfeeding, the benefits of breastfeeding likely outweigh potential risk associated with these chemicals. Breast milk contains significant amounts of iodine that will likely reduce the ability of NIS inhibitors (e.g. perchlorate and thiocyanate) to block adequate iodide uptake by the thyroid. Indeed, the breast fed infants we studied were iodine-sufficient (median urinary iodide 129.5 μg/L), and thus it was less likely that exposure to NIS inhibitors resulted in inadequate iodine uptake by the thyroid. In addition to improving health by nutritional benefits, breast feeding offers immunological, developmental, psychological and economic advantages (35–38). For these reasons, the American Academy of Pediatrics recommends breast feeding (39).

In summary, this study of a convenience sample of infants provides novel data relevant to infant exposure to perchlorate, nitrate and thiocyanate. Our urine-based perchlorate dose estimates are consistent with previously published estimates that were based on dietary intakes. The magnitude of perchlorate exposure dose varies by feeding method: breast-fed infants had higher perchlorate doses than infants who consumed cow milk-based formula, and soy formula-fed infants had the lowest estimated perchlorate doses. The adjusted average perchlorate dose estimated for all infants in our study (0.255 μg/kg/day) is below the reference dose, however 16% of all infants (and 31% of breast-fed infants) had at least one perchlorate exposure dose in excess of the reference dose. The health impact of these perchlorate exposures is unknown. Regression models of this dataset indicate that urinary levels of perchlorate and thiocyanate were associated with increased urinary TSH in infants with iodide levels < 100 μg/L (7) which is consistent with previous findings in U.S. women (6). However, modeling of urinary thyroxine levels found that urinary perchlorate was associated with increased urinary thyroxine (7), instead of the decreased thyroxine that would be biologically coherent with inhibition of thyroxine synthesis by inhibiting iodide uptake. Additionally, the small study size limits our ability to differentiate between the effects of perchlorate and feeding method. Additional studies are needed to characterize the health impact of exposure of infants to perchlorate and related anions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was partially supported by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences

Literature Cited

1. Mendiratta, SK.; Dotson, RL.; Brooker, RT. Perchloric Acid and Perchlorates. New York, NY: John Wiley & Sons, Inc; 2005. p. 157-70.
2. Dasgupta PK, Martinelango PK, Jackson WA, et al. The origin of naturally occurring perchlorate: the role of atmospheric processes. Environ Sci Technol. 2005; 39:1569–75. [PubMed: 15819211]

3. Rao B, Anderson TA, Orris GJ, Rainwater KA, Rajagopalan S, Sandvig RM, Scanlon BR, Stonestrom DA, Walvoord MA, Jackson WA. Widespread natural perchlorate in unsaturated zones of the southwest United States. Environ Sci Technol. 2007; 41:4522–8. [PubMed: 17695891]
4. 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; 110:927–37. [PubMed: 12204829]
5. Wyngaarden JB, Stanbury JB, Rapp B. The effects of iodide, perchlorate, thiocyanate and nitrate administration upon the iodide concentrating mechanism of the rat thyroid. Endocrinology. 1953; 52:568–74. [PubMed: 13060263]
6. Blount BC, Pirkle JL, Osterloh J, Valentín-Blasini L, Caldwell KL. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect. 2006; 114:1867–71.
7. Cao Y, Blount BC, Valentin-Blasini L, Bernbaum JC, Phillips TM, Rogan WJ. Goitrogenic Anions, Thyroid Stimulating Hormone, and Thyroid Hormone in Infants. Environmental Healt Perspectives. 2010; 118:1332–1337.
8. Blount BC, Valentín-Blasini L, Mauldin JP, Pirkle JL, Osterloh JD. Perchlorate exposure of the U.S. population, 2001–2002. J Expo Sci Environ Epidemiol. 2007; 17:400–7. [PubMed: 17051137]
9. U.S. Environmental Protection Agency. Terms of Environment: Glossary, Abbreviations and Acronyms. Available at http://www.epa.gov/ncea/iris/help_gloss.htm#r
10. Baier-Anderson C, Blount BC, LaKind JS, Naiman DQ, Wilbur SB, Tan S. Estimates of exposures to perchlorate from consumption of human milk, dairy milk, and water, and comparison to current reference dose. J Toxicol Environ Health, Part A. 2006; 69:319–30. [PubMed: 16407090]
11. Ginsberg G, Hattis DB, Zoeller RT, Rice DC. Evaluation of the U.S. EPA/OSWER preliminary remediation goal for perchlorate in groundwater: Focus on exposure to nursing infants. Environ Health Perspect. 2007; 115:361–369. [PubMed: 17431484]
12. Kirk AB, Dyke JV, Martin CF, Dasgupta PK. Temporal patterns in perchlorate, thiocyanate, and iodide excretion in human milk. Environ Health Perspect. 2007; 115:182–6. [PubMed: 17384762]
13. Dasgupta PK, Kirk AB, Dyke JK, Ohira S. Intake of iodine and perchlorate and excretion in human milk. Environ Sci Technol. 2008; 42:8115–8121. [PubMed: 19031911]
14. Murray CW, Egan SK, Kim H, Beru N, Bolger PM. US Food and Drug Administration's Total Diet Study: Dietary intake of perchlorate and iodine. J Expo Sci Environ Epidemiol. 2008; 18:571–580. [PubMed: 18167505]
15. NRC. Health Implications of Perchlorate Ingestion. Washington. D.C: National Research Council, National Academy Press; 2005.
16. Tran N, Valentin-Blasini L, Blount BC, Gibbs C, Fenton MS, Gin E, Salem A, Hershman JM. Thyroid-stimulating hormone increases active transport of perchlorate into thyroid cells. Am J Physiol Endocrinol Metab. 2008; 294:E802–E806. [PubMed: 18303123]
17. Cao Y, Calafat AM, Doerge DR, Umbach DM, Bernbaum JC, Twaddle NC, Ye X, Rogan W. Isoflavones in urine, saliva, and blood of infants: data from a pilot study on the estrogenic activity of soy formula. J Expo Sci Environ Epidemiol. 2009; 19:223–34. [PubMed: 18665197]
18. Valentín-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; 1155:40–6. [PubMed: 17466997]
19. Caudill SP, Schleicher RL, Pirkle JL. Multi-rule quality control for the age-related eye disease study. Stat Med. 2008; 27 (20):4094–4106. [PubMed: 18344178]
20. Taylor, JK. Quality Assurance of Chemical Measurements. New York: Lewis Publishers; 1987.
21. Mage DT, Allen RH, Kodali A. Creatinine corrections for estimating children's and adults' pesticide intake doses in equilibrium with urinary pesticide and creatinine corrections. J Expo Sc Environ Epidemiol. 2008; 18:360–368. [PubMed: 17878925]
22. Anderson M, de Benoist B, Delange F, Zupan J. WHO Secretariat on behalf of the participants to the consultation. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutr. 2007; 10:1606–1611. [PubMed: 18053287]

23. Delange F, Heidemann P, Bourdoux P, Larsson A, Vigneri R, Klett M. Regional variations of iodine nutrition and thyroid function during the neonatal period in Europe. Biol Neonate. 1986; 49:322–330. [PubMed: 3756256]
24. Dlouhy P, Rambouskova J, Wiererova O, Pokorny R, Bilek R, Kubisova D, Prochazka B, Andel M. Iodine saturation in Roma neonates in Prague is not at an optimum level. Ann Nutr Metab. 2006; 50:242–246. [PubMed: 16508251]
25. Dorey CM, Zimmermann MB. Reference values for spot urinary iodine concentrations in iodine-sufficient newborns using a new pas collection method. Thyroid. 2008; 18:347–352. [PubMed: 18341380]
26. Rassin DK, Gaull GE, Raiha NCR, Heinonen K, Jarvenpaa A. Protein Quantity and Quality in Term and Preterm Infants: Effects on Urine Creatinine and Expression of Amino Acid Excretion Data. J of Pediatric Gastroenterology and Nutrition. 1986; 5:103–110.
27. Pearce EN, Leung AM, Blount BC, Bazrafshan HR, He X, Pino S, Valentín-Blasini L, Braverman LE. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. J Clin Endocrinol Metab. 2007; 92:1673–7. [PubMed: 17311853]
28. Schier JG, Wolkin AF, Valentín-Blasini L, Belson MG, Kieszak SM, Rubin CS, Blount BC. Perchlorate exposure from infant formula and comparisons with the perchlorate reference dose. J Expo Sci Environ Epidemiol. 2009 In press.
29. Kirk AB, Smith EE, Tian K, Anderson TA, Dasgupta PK. Perchlorate in milk. Environ Sci Technol. 2003; 37:4979–81. [PubMed: 14620826]
30. U.S. Environmental Protection Agency. Perchlorate and Perchlorate Salts. Available at http://www.epa.gov/IRIS/subst/1007.htm
31. Daniels AL, Hejinian LM. Growth in infants from the standpoint of physical measurements and nitrogen metabolism. American Journal of Dis Child. 1929; 37:1128–1138.
32. Stearns G, Newman KJ, McKinley JB, Jeans PC. The protein requirements of children from one to ten years of age. Ann NY Aca Sci. 1957; 69:857–868.
33. Viteri FE, Alvarado J. The creatinine height index: its use in the estimation of the degree of protein depletion and repletion in protein calorie malnourished children. Pediatrics. 1970; 46:696–706. [PubMed: 5529692]
34. Arcus-Arth A, Krowech G, Zeise L. Breast milk and lipid intake distributions for assessing cumulative exposure and risk. J Expo Anal Environ Epidemiol. 2005; 15:357–365. [PubMed: 15562290]
35. Hanson LA, Adlerberth I, Carlsson B. Protective factors in milk and the development of the immune system. Pediatrics. 1985; 75:172–176. [PubMed: 3880886]
36. Lawrence RM, Lawrence RA. Given the benefits of breastfeeding, what contraindications exist? Pediatrics Clinics of North America. 2001; 48:235–251.
37. Lawrence R. Breastfeeding: benefits, risk and alternatives. Obstetrics and Gynecology. 2000; 12:519–524.
38. Department of Health and Human Service Office on Women's Health. Benefits of Breastfeeding. Nutr Clin Care. 2003; 6:125–131. [PubMed: 14979457]
39. AAP (American Academy of Pediatrics). Section on Breastfeeding. Breastfeeding and the Use of Human Milk. Pediatrics. 2005; 115:496–506. [PubMed: 15687461]

Environ Sci Technol. Author manuscript; available in PMC 2012 May 1.

Table 1

Adjusted[a] concentrations of perchlorate, nitrate, thiocyanate, iodide and creatinine in urine samples collected from infants consuming breast milk, cow milk based formula or soybased formula.

	Perchlorate[†] (μg/L)	Nitrate[†] (μg/L)	Thiocyanate[†] (μg/L)	Iodide[†] (μg/L)	Creatinine (mg/dL)
Breast Milk (N[b]=92)					
Mean	4.97[c]	18350	189[f]	279	12.99
Median	3.9	14150	98.1	129.5	8.5
Range	<0.05–25.8	<500–123000	<10–1240	18.8–5210	2.7–82.9
Geo Mean	2.65	8697	95.6	132.3	9.42
% Detect	95	85	98	100	100
Cow Milk Based Formula (N=51)					
Mean	2.89[d]	29330[e]	151[g]	199 [h]	18.50[i]
Median	2.2	19800	81.2	151	13.6
Range	<0.05–13.1	<500–191000	<10–1300	19.8–841	2.7–70.9
Geo Mean	1.3	12215	87.2	152.6	14.05
% Detect	86	86	98	100	100
Soy Based Formula (N=63)					
Mean	1.07	32070	70	162	17.23
Median	0.58	19500	21.9	108	11.6
Range	<0.05–5.49	<500–127000	<10–1150	4.62–509	3.5–76.3
Geo Mean	0.35	15679	26.9	105.4	13.17
% Detect	68	87	84	100	100

[a] Urinary analyte concentrations adjusted for diaper contamination of perchlorate (1.24 μg/L), age, sex and BMI.

[b] N = number of individual urine samples.

[c] Breast-fed infants have significantly higher urinary perchlorate concentrations than do infants consuming cow milk based formula ($p = 0.004$) or soy-based formula ($p < 0.001$).

[d] Infants consuming cow milk based formula have significantly higher urinary perchlorate concentrations than do infants consuming soy-based formula ($p < 0.001$).

[e] Infants consuming cow milk based formula ($p=0.017$) and soy-based formula ($p=0.005$) have significantly higher urinary nitrate concentrations than breast-fed infants.

[f] Breast-fed infants have significantly higher urinary thiocyanate concentrations than do infants consuming soy-based formula ($p < 0.001$).

[g] Infants consuming cow milk based formula have significantly higher urinary thiocyanate concentrations than do infants consuming soy-based formula (p =0.006).

[h] Infants consuming cow milk based formula have significantly higher urinary iodide concentrations than do infants consuming soy-based formula (p =0.003).

[i] Infants consuming cow milk based formula have significantly higher urinary creatinine concentrations than breast-fed infants (p =0.03).

[†] Mean and geometrical mean adjusted for age, sex and BMI in mixed linear model.

Environ Sci Technol. Author manuscript; available in PMC 2012 May 1.

Table 2

Estimated perchlorate dose (μg/kg/day) for 205 urine samples collected from 92 infants at ages ranging from 1–377 days.*

	All Infants	Feeding Groups		
	Perchlorate dose (μg/kg/day)	**Breast Milk**	**Cow milk formula**	**Soy Formula**
N[a]	205	91	51	63
Mean†	0.255	0.420	0.208	0.065
Median	0.160	0.315	0.160	0.039
Maximum	1.843	1.843	1.396	0.352
Geo Mean†	0.0922	0.220	0.103	0.027

[a] number of urine samples.

* data adjusted to account for 1.24 μg/L perchlorate contamination from diapers

† Adjusted for age, sex and BMI in mixed linear model.