Intake of Iodine and Perchlorate and Excretion in Human Milk

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Perchlorate, thiocyanate, and iodine excretion in urine and milk of 13 breastfeeding women was investigated and the results were interpreted by a model of parallel/competitive transport of these species by the sodium iodide symporter. For each species $i$, we assumed physiological homeostasis, where $f_{in}$ equals the corresponding total excretion in urine and milk $(k_{in} + f_{in,m})$. The fraction of the total excretion that appeared in milk $f_{in,m}$ was measured and ranged from 0.394–0.781, 0.018–0.144, and 0.086–0.464 for perchlorate, thiocyanate, and iodine, respectively. The corresponding median values were 0.541, 0.053, and 0.177, respectively. The selectivity factors of perchlorate over iodide transport, and thiocyanate over iodide transport, defined as $f_{PC,m}/f_{I,m}$ and $f_{SCN,m}/f_{I,m}$, respectively, were 3.14 ± 1.20 and 0.27 ± 0.26 while $P_{IT,m}$, $SCN_{IT,m}$, and $f_{I,m}$ among individuals varied 4.9, 5.0, and 8.4, respectively. These transport selectivities are an order of magnitude lower than those indicated by in vitro experiments. On the other hand, ingested thiocyanate is known to be oxidized by a variety of mechanisms (14) and forms various adducts (15). Of interest is that thiocyanate also has benefits: its lactoperoxidase-mediated oxidation products are powerful antibacterial agents (16–18) and in infants may provide protection against the human immunodeficiency virus (19).

There is no universal agreement on the extent of threat posed by perchlorate in breast milk (20–23). There is also no conclusive data as to if and to what extent perchlorate inhibits iodide transport to human milk. Extrapolation from mouse NIS experiments to a human mother–infant pair is tenuous, especially when such in vitro experiments involve concentrations far removed from reality and perchlorate is known to be transported through the NIS in a manner different from that of iodide (6).

In the present paper, we try to ask this question with a cohort of breastfeeding mothers: Does perchlorate inhibit iodide transport to milk? If so, with what selectivity factor and how much does it vary among individuals?

Experimental Section

Cohort. Fifteen lactating women participated in the study, having given informed consent under a protocol approved by the University of Texas at Arlington. The prelabeled sampling kit given to subjects contained a waterproof pen for recording sample information directly on the appropriate tube. Thirteen sample sets were returned following instructions but the completeness of the sample sets varied (see Supporting Information (SI) for details). The 14th sample set was labeled by the participant with water-labile ink that became illegible and mostly could not be used. The 15th participant was found to have substituted formula for at least one of the purported breast milk samples; we chose to discard the entire sample set. Donors were 24–34 years old; one was Hispanic, one was Asian, and one described herself as of both Asian and Caucasian origin; the rest were Caucasian. No subjects reported smoking or living with a smoker. The participants were specifically asked and reported not taking any prescription medicine, having no known thyroid disease or taking any form of a thyroid medication. Donors were in varying stages of lactation with infants ranging in age from 55–253 days (on the first sample collection day). These and

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other details of the cohort, including iodized salt use status, are noted in Table S1 in the SI.

Sample Collection. Each subject was provided with a prelabeled kit with tubes color-coded for different sample types (50 mL capacity capped polypropylene centrifuge tubes, P/N 89004-364, VWR Scientific, all from one manufacturer lot) and 24 h urine collection bottles (high density polyethylene, P/N 82028-222, VWR). Iodide, thiocyanate, and perchlorate were measured in replicate in container extracts; collection tubes were extracted with 10 mL of ultrapure water, and 24 h urine collection bottles were extracted with 500 mL of ultrapure water. Iodine and thiocyanate content in both extracts were below the respective limits of detection (LOD) of 0.1 and 0.01 µg/L. Perchlorate concentration in the urine collection bottles was also below the LOD of 0.005 µg/L. Perchlorate concentration in the 10 mL collection tube extracts averaged 0.17 ± 0.035 µg/L (n = 5), the highest measuring 0.216 ± 0.073 µg/L. Because sample volumes were usually larger than 10 mL and the determined perchlorate concentrations much higher, no efforts were made to subtract blank values.

Ideally, the subjects collected 9 sets of milk and urine samples on consecutive days or without major gaps; with a single set comprising a 24 h urine sample along with four breast milk samples collected at different times on that same day; specific time requirements for milk sampling were not imposed. All subjects collected milk samples with breast pumps. They were asked to alternate between fore and hind milk collections, if practical. While most complied with instructions and we received sample sets worth 9 days, the range of usable samples from individual subjects varied from 3 to 10 days. Details are presented in the SI.

Urine samples were collected by urinating directly into a urine collection bottle from the second micturition to the following day’s first micturition. Total urine volume was recorded on a sample record sheet. After shaking to mix, a ∼40 mL subsample was transferred to a collection tube on which the total volume was recorded. This was frozen without addition of preservatives; the rest was discarded.

All samples were frozen in the donors’ home freezers as soon as possible after collection. Subjects contacted us to request that samples be picked up either at the completion of sample collection or earlier if desired. Samples were transported on dry ice to our facility, and stored at −20 °C until processed and analyzed.

Analytical Methods. Milk. Samples were spiked with quadruply 18O labeled perchlorate ([35Cl18O4]) and 129I-labeled iodide, amounting to 5 and 10 µg/L in concentration, respectively, to act as internal standards for isotope dilution mass spectrometry (IDMS). Milk was processed according to Dyke et al. (24). The samples were analyzed for perchlorate, iodide, and thiocyanate using a TSQ Quantum Discovery Max MS/MS using a heated electrospray ionization probe (Thermo). Chromatography was performed using 25-µL filled loop injections on a Dionex DX-600 ion chromatograph on 2 mm AG-16/AS-16 column sets with a 60 mM KOH eluent at 0.25 mL/min before analysis by MS/MS. Iodide eluted at 6.6 min, SCN− eluted at 8.9 min, and perchlorate eluted at 10.9 min. The column effluent was diverted to the MS from 4.7 to 14 min. Analyte perchlorate was monitored by the mass transition of ml/z 99 → ml/z 83 ([35Cl18O4]− → [35Cl16O3]−). The internal standard was quantitated by the mass transition of ml/z 107 → ml/z 89 ([35Cl18O4]− → [35Cl16O3]−). Thiocyanate was monitored without fragmentation: ml/z 58 → 58 using [35Cl18O4]− as the internal standard. We experimented with 13C-labeled thiocyanate but given 1.1% natural abundance of 13C, a significant response was already present at this ml/z, to compensate for which a relatively large concentration of the expensive isotopically labeled internal standard had to be added. Compared to the use of labeled thiocyanate, the use of [35Cl18O4] as internal standard for thiocyanate determination produced results within ±15% and was henceforth used. Samples were analyzed for total iodine using an X Series II ICP-MS equipped with a Peltier-cooled nebulizer (Thermo). 127I and 129I were monitored in the “peakjump” mode using vendor-supplied software; each isotope was monitored for 50 ms and 200 sweeps were performed.

Urine. Perchlorate internal standards for IDMS (5 µg/L) were first added. The spiked samples were passed through a cation exchange resin column in H+ form (Dowex 50Wx8, ~5 g), then pH adjusted to ~10 with ammonium hydroxide and passed through a basic alumina column (~0.5 g) and filtered with a 0.45 µm pore size membrane filter. Samples were analyzed for perchlorate and thiocyanate by MS/MS in much the same manner as for milk. For urinary iodine analysis, samples were first filtered through a 0.45 µm pore size membrane filter (the material retained by the filter was checked to have contained no iodine within our limits of detection). The filtrate was diluted 20-fold and 129I-iodide was added to attain a concentration of 10 µg/L as an internal standard for IDMS and analyzed for total iodine using ICP-MS (X Series II, Thermo).

Urinary creatinine was measured by a kinetic adaptation of the spectrophotometric Jaffe method (25).

Model: Methods of Estimation of Excretion Amounts and Calculation of Selectivity. The data we have available are not by themselves sufficient for a physiologically based pharmacokinetic model. As a first approximation, we invoke a standard parallel/competitive reaction model widely used in chemical kinetics (26) where A reacts independently with B, C, D, etc. individually to produce E, F, G, respectively. Here we assume that the role of the common reagent A is catalytically played by the NIS (it is not itself consumed). We assume that homeostasis prevails: total input and output of any of the analytes of interest are equal. We assume NIS transport processes to take place in a steady state, a constant steady state input concentration, B0, C0, D0, etc., of B, C, D (e.g., iodide, perchlorate, thiocyanate, etc., respectively) are maintained in circulation. We further assume that these steady state concentrations are linearly proportional to the total 24 h excretion (in milk and urine combined) of each respective analyte. The rate at which E is formed from B is thus proportional to [A]B0. If B represents iodide and E is the iodide that has been transported into milk, the amount of iodine in excreted in milk over 24 h, Ie,m, can be written as

\[ I_{e,m} = k[A](I_{e,m} + I_{e,u}) \] (1)

where \( I_{e,m} \) is the amount of iodide excreted in urine during the same period and \( B_0 \) is proportional to \( I_{e,m} + I_{e,u} \). \( k_I \) is a transport constant that includes this foregoing proportionality and \( [A] \) is a measure of the extent of NIS expression. Eq 1 is readily transposed to eq 2, where \( f_{e,u} \) denotes the fraction of the total excretion of species i that is excreted in milk.

\[ I_{e,m}/(I_{e,m} + I_{e,u}) = f_{e,m} = k_I[A] \] (2)

One similarly writes

\[ PC_{e,m}/(PC_{e,m} + PC_{e,u}) = f_{PC,m} = k_{PC} [A] \] (3)

We define the selectivity with which perchlorate is transported over iodide as

\[ S_{PC/I} = f_{PC,m}/f_{e,m} = k_{PC} / k_I \] (4)

Effectively, the selectivity is thus a ratio of these transport constants. \( S_{PC/I} \) is similarly defined.

The total daily urinary excretion for species i (\( I_{e,u} \), is readily computed from the volume of the composite 24 h urine sample (\( V_{u,24} \)), and the measured analyte urine concentrations, \( I_e \):

\[ I_{e,u} = V_{u,24}I_e \]
where \( i \) is I, PC, or SCN.

It is less straightforward to measure the corresponding milk excretion values; this must remain an estimate. Within a single day, the concentrations of these analytes in milk can vary significantly with respect to trace analyte content (27). Thus, a single sample is inadequate. We estimated milk excretion by taking the respective average analyte concentrations ([\( m_{i,m} \)]) of the milk samples collected on that day. These average analyte concentration data were multiplied by the volume of milk (\( V_{m,24} \)) that an average infant of that particular age consumes per day, as interpolated from the detailed age-dependent average milk consumption data listed by Neville et al. (28); this varies between 0.600 and 0.813 L for the age of the infants in our study. The daily excretion of each analyte in milk (\( e_{i,m} \)) was thus calculated:

\[
 e_{i,m} \mu g = V_{m,24} \mu L \times [m_{i,m}] \mu g / \mu L
\]  

Homeostasis was assumed: the sum of the urinary and milk outputs equals total intake (\( T_{i,n} \)):

\[
 T_{i,n} \mu g = e_{i,m} \mu g + k_{e,m} \mu g
\]

For each day, for each participating subject, we calculated \( f_{i,m} \) values for \( i = I, PC, \) and SCN. The averages and standard deviations for all three \( f_{i,m} \) values for each subject are listed in Table 1.

**Results and Discussion**

The objective of the present study was to study the excretion of perchlorate, thiocyanate, and iodide in milk and urine and relate the observed pattern within the broad framework of parallel/competitive transport by the NIS. The basic assumption is that the mammary NIS represents a controlled selective gate through which all three ions are expressed and the remainder of the intake is excreted in urine. We have admittedly neglected some other routes of excretion. The fecal excretion of iodide has been reported to be 1.2% of total excretion of iodide (29). Iodide is also lost in sweat but data on this are scarce. It is not clear that this route of loss is significant except in a situation where profuse sweating is induced, e.g., when major physical exertion is carried out in a hot environment (30).

**Sample Numbers and Analysis.** To resolve any ambiguities as to whether noniodide forms of iodine are excreted in either urine or milk, we used ICP-MS rather than IC-MS/MS data for iodine. Within experimental error, the two methods produced essentially the same values, suggesting that iodide is essentially the only form of iodine in both urine and milk; this aspect is not discussed here. While a cohort of thirteen may seem small, note that our analysis and discussion are based on 402 separate milk samples and 103 24-h urine samples (each analyzed by IC-MS/MS for three analytes and by ICP-MS for iodine). Each sample was analyzed in duplicate and if the results were more than 5% different from each other, the sample was analyzed a third time; averages are reported in all cases. All analytes in all samples were far above the LOD (0.1, 0.005, and 0.01 \( \mu g / L \) for \( I^- \), \( \text{ClO}_4^- \), and \( \text{SCN}^- \) by IC-MS/MS and 0.1 \( \mu g / L \) by ICP-MS); typical analytical precision ranged between 2 and 2.5%.

A large number of samples were needed for any given individual because previous studies suggested considerable within-day and between-day variations (27). We conducted pilot studies to see how well creatinine (CR) adjustment of spot urine samples can predict 24-h excretion. Such studies, to be discussed elsewhere, showed that CR adjustment could not properly predict 24-h iodine excretion and 24-h samples had to be collected.
Creatinine. Mean urinary CR excretion in our cohort was 0.894 ± 0.486 g/day and fell at the low end of the reference range of 1.26 ± 0.21 g/day (31) for adult women. However, no reference values exist specifically for lactating women. Creatinine has been reported in milk although most of these data are quite dated (32–34). The most recent analysis of breast milk for CR was reported to be 52 μM or 7.8 mg/L (35). Assuming on the average <1 L milk production, milk is unlikely to be a significant excretory pathway for CR. Arguably, some subjects may not have followed instructions and the 24-h urine collections were not complete. Bingham et al. (36) suggested <0.6 g of CR in a 24-h urine collection to be indicative of an incomplete collection. We had three subjects, one averaged exactly at the borderline and the two others averaged 0.54 g/d, respectively. Since these are borderline and there are no real guidelines specifically for lactating women, we have marked these subjects as such in the data presented in Table 1, rather than omitting them altogether. Six of the individual 24-h urine collections also exceeded the high limit of the reference range. Animal protein intake can increase urinary CR. For children, animal protein intake must be taken into account when urinary CR is used for adjustment of excretion data (37). In cattle, it is long known that urinary CR does increase with protein intake (38). Further research would be necessary to characterize a reference range specifically for lactating women.

Perchlorate and Iodide Doses and Relationships. Table 1 presents data on the average fT,in for each of the three species for each subject during the study period and fPC,m along with the standard deviations. According to the Institute of Medicine (IOM (39)), for 0–6 month and 6–12 month olds, adequate intake (AI) of iodine is 110 and 130 μg/d, respectively. Four infants at the time of the study were aged between 6 and 12 month category; all others were younger (Table S1, S1). The individual data (few subjects) showed that only one out of thirteen infants in this study receives iodine that would be judged adequate. The results for the bottom half of the pool give cause for concern: the infants are getting 12, 16, 19, 19, 22, and 29% of the IOM suggested AI values. We would also point out that relative to virtually all other previous studies carried out with spot samples, this is the first study involving multiple samples on sequential days and should thus provide a better measure of iodine nutrition, albeit for a very limited cohort. Coupled to the iodine nutrition situation is the perchlorate intake. The National Academy of Science (NAS) panel has opined that the reference safe dose for perchlorate is 0.7 (NAS) panel has opined that the reference safe dose for perchlorate is 0.7 µg/kg/d (40). The weight of each infant was estimated by the tabulated gender specific age-dependent percentile infant weight data (41). The dose for each infant was calculated. In 9 out of 13 cases, the reference dose was exceeded, in the worst case, by 3×.

When we examine the fraction of fPC,in (range 0.394–0.781; mean(±SD) 0.562 ± 0.116) relative to fT,in (range 0.086–0.451; mean(±SD) 0.210 ± 0.108), it becomes obvious that perchlorate is excreted to a much greater degree in milk than is iodine. No relationships between infant age and SCN,m. This is again consistent with the argument that thiocyanate in urine may have independent and variable sources. Figure S1 (SI) shows plots of fPC,m vs fT,in for all three species. The correlations are weak and possible implications are discussed therein.

Transport Selectivity of Perchlorate over Iodide. The effective selectivity of perchlorate over iodide transport $S_{PC/I}$ (Table 1, column 9/column 6) is shown in Figure 2 for each individual along with one standard deviation error bars. While there is some variation in the $S_{PC/I}$ values determined in each day for each individual (the relative standard deviation (RSD) is lowest for donor 2 and highest for donor 6; and no significant correlation of the RSD with the absolute magnitude of $S_{PC/I}$ was found), it is to be noted that in terms of daily total excretions across individuals, the iodine excretion varied by $>15×$, and the perchlorate excretion varied by $>30×$. Even after the data are averaged for each individual, these total excretions vary by $>9×$ and $<5×$, respectively. Under these circumstances, the average computed $S_{PC/I}$ value of 3.14 ± 1.20 across all individuals is remarkably constant. This value is $<10×$ lower than the selectivity factor of 30 reported by Tonacchera et al. (5). Both the Tonacchera et al. and Dohan et al. (6) experiments were generally conducted with high levels of transported ion concentrations where NIS availability may become a limiting factor. Such a situation may not prevail in vivo, either due to changing NIS expression as hormone levels and ratios change, or because of variation in the structure and properties of different mammalian NIS systems (44).

Perchlorate and Iodide in U.S. Mothers. The levels of iodine and perchlorate in milk found in this study is compared to those reported in previous studies on U.S. mothers by us.
TABLE 2. Milk and Urine Perchlorate and Iodine Content of Breastfeeding Mothers

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<th>N</th>
<th>range µg/L</th>
<th>average (SD) µg/L</th>
<th>geometric mean↑ (SEM↑range) µg/L</th>
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a All results rounded to two significant figures. b Total number of samples. In ref 27 and this work, multiple samples have come from each individual. c Generally closer to the median than arithmetic mean; given for comparison as only parameter given in ref 45. d Standard error of the mean, range is ± 1 SEM. e All other data from U.S.; this study was in Denmark, no perchlorate was measured. f Nonsmokers, all subjects in refs 3 and 27 and the present study were also nonsmokers. g Smokers; a minority of subjects in ref 43 were smokers but the data are pooled together here. h Data not available.
concentrations of perchlorate and one containing very high iodine concentration (not in the plot) in the Pearce et al. (43) study, the spread of the data from the different studies do substantially overlap. The median urinary iodine values agree closely between this study (43) and the study reported in ref 47. The median urinary perchlorate values also agree closely between this study and ref 43 but 46 has a lower value. Median breastmilk perchlorate value is only marginally higher in 43 compared to this study but median breastmilk iodine is much higher in 43. While the median or average values of both perchlorate and iodide concentrations in ref 43 are significantly higher, both the present study and that in 43 were largely regional, underscoring the need for a large, nationwide study. In the U.S. Food and Drug Administration’s Total Diet Study (48), 25–30 and 40–45 year old women were estimated to have a daily intake of 5.4–6.8 and 5.9–7.3 μg of perchlorate and 148–196 and 145–197 μg of iodine, respectively. This substantially underestimates the median daily perchlorate intake (excretion) of our cohort. At 223 μg/d, the iodine intake (excretion) of our cohort is also slightly higher than that predicted above, but both are substantially lower than the desired value of 290 μg/d.

When we first pointed out the widespread occurrence of perchlorate in U.S. mother’s milk (3), we were criticized (22) for the statement regarding a breast milk iodide vs perchlorate plot that it is remarkable that not a single datum fell within the high perchlorate high iodide quadrant. After several hundred milk analyses later, albeit without the benefit of any lines drawn to define “high” and “low”, not a single datum still falls in the high perchlorate—high iodide sector, most obvious from Figure 3b. This continues to suggest that in real mothers perchlorate does inhibit the transport of iodine into milk and because of competitive inhibition both analytes cannot be high at the same time.

Even though the number of subjects was not large, in terms of the number of total samples analyzed, this is the most extensive study on the topic. The majority of the infants in our study ingested perchlorate at a level that exceeds the NAS reference dose. It is not clear how and if the NAS reference dose takes into account iodine intake, or for that matter the perchlorate/iodide selectivity of the NIS. While the reference dose thus remains a gray area, we were intrigued, and dismayed, to note that while little of the maternal iodine (21.0 ± 10.8%) finds its way to milk, the bulk of the perchlorate intake (56.2 ± 11.6%) ends up in milk. The low iodine intake in this small cohort of breastfed U.S. infants is disconcerting. It is doubtful that these infants would have received adequate levels of iodine even without the influence of iodide transport inhibitors. Most of the donors in this study came from the local metropolitan area. We will report on this elsewhere in more detail but our analysis of their drinking water generally did not indicate drinking water to be a major contributor to their perchlorate intake.

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Supporting Information Available
Table of cohort description, sample details and irregularities, figure showing fraction of each species transported in milk as a function of the total intake and accompanying description. This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited


(24) United States Environmental Protection Agency. Child-Specific Exposure Factors Handbook; EPA-600-P-00-002B; Washington, DC, 2002; Table 11–1.


