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Early-life exposure to lithium and boron from drinking water

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ABSTRACT

The transfer of lithium and boron from exposed mothers to fetuses and breast-fed infants was investigated in areas in northern Argentina and Chile with up to 700 μg lithium/L and 5–10 mg boron/L in drinking water. Maternal and cord blood concentrations were strongly correlated and similar in size for both lithium (47 and 70 μg/L, respectively) and boron (220 and 145 μg/L, respectively). The first infant urine produced after birth contained the highest concentrations (up to 1700 μg lithium/L and 14,000 μg boron/L). Breast-milk contained 40 and 60% of maternal blood concentrations of lithium and boron, respectively (i.e. about 30 and 250 μg/L, respectively, in high exposure areas), and infant urine concentrations decreased immediately after birth (120 μg lithium/L and 920 μg boron/L). We conclude that lithium and boron easily passed the placenta to the fetus, and that exclusively breast-fed infants seemed to have lower exposure than formula-fed infants.

1. Introduction

Lithium (Li), an alkali metal (atomic weight 6.9), and boron (B), a light (atomic weight 10.8) non-metallic trace element, are found in rocks, soil and water at varying concentrations. Lithium concentrations in drinking water between <1 and 170 μg/L were found in Texas [1], Japan [2] and England [3], while concentrations exceeding 1000 μg/L were reported from Austria [4], northern Chile [5], and northern Argentina [6]. Boron concentrations in drinking water of <1–1000 μg/L were detected in California, Germany and France [7,8], and from 6000 to 15,000 μg/L in northern Argentina [6] and Chile [7,9]. However, none of the elements are included in the regular drinking water control. To our knowledge, only Russia and Ukraine have standard values for lithium in drinking water (30 μg/L) [10]. The provisional guideline value for boron in drinking water established by the World Health Organization (WHO) is 2400 μg/L based on an estimated No Observed Adverse Effect Level (NOAEL) of 9.6 mg B/kg body weight/day from experimental animal studies [11,12]. Concerning food, grains and vegetables, in particular spinach, seem to have the highest concentrations of lithium (0.5–4.6 μg/g) [13,14], and certain seafood, fruits, nuts, legumes and vegetables, the highest concentrations of boron [12].

Lithium has long been used in the treatment for bipolar disease, and lithium therapy during pregnancy has been associated with several adverse effects in the offspring, e.g. cardiac malformations, hypothyroidism, kidney impairment, low Apgar scores, as well as central nervous system and neuromuscular complications [15–17]. It is suggested that lithium passes freely from serum to breast milk, but there is a wide variation in reported concentrations (700–3500 μg/L) in breast milk of mothers on lithium therapy [18,19]. To the best of our knowledge, there are no studies evaluating the early-life exposure and potential health effects of lithium through drinking water.

Studies in rats, mice and rabbits showed that high boron exposure caused low birth weight and teratogenicity, indicating that fetal growth, lumbar and thoracic ribs, and the cardiovascular system could be the most sensitive targets for developmental toxicity of boron [12,20]. However, there are very few data available on the extent of early life boron exposure. Two studies showed concentrations in breast milk of 30–40 μg/L in Canadian women [21] and 250–300 μg/L in women from Missouri [22]. In none of these studies was the exposure identified.

Because of the observed elevated concentrations of lithium and boron in drinking water in some areas and the possible risk of adverse effects early in life, the present study aimed to evaluate the transfer of lithium and boron from environmentally exposed mother to the fetus and breast-fed infant.

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2. Materials and methods

2.1. Study areas

Three small mother–child cohorts were considered in this study. The first was recruited in 1996 ($N = 11$) in San Antonio de los Cobres, Northwestern Argentina, while two were recruited in 2010 in Chile: one in Arica in the North ($N = 24$), and one in Santiago, the control area ($N = 11$).

San Antonio de los Cobres with about 6000 inhabitants is located at around 3800 m above the sea level in the western part of the Province of Salta. We have previously demonstrated that the public drinking water, supplied from a natural spring outside the village, has about 200 μg/L of arsenic [23], which seems to remain stable over time [6,24]. Using modern inductively coupled plasma mass spectrometry (ICP-MS) instrumentation, we recently discovered that the water also contains about 1000 μg/L of lithium and 6000 μg/L of boron [6]. The diet in the Puna area is largely of animal origin (meat and milk products, and commonly no fish), accompanied with vegetables, potatoes, maize, and rice. According to the hospital statistics, about 200 children are born every year in San Antonio de los Cobres and 5 surrounding villages within the Andean Puna, and there is an overall infant mortality rate of about 41 per 1000 born infants [25]. This rate has remained about the same for the last 20 years.

The northern Chilean study was carried out in Cerro Chuño and Los Industriales neighborhoods (15,000 inhabitants), both located in the periphery of Arica, a city close to the border with Peru. The drinking water in Arica is taken from the Lluta river and a lake in Azapa Valley [9], with reported concentrations of about 1500 μg/L lithium and 1000 μg/L boron, respectively [5,26]. For comparison, mother–child pairs were also recruited in Santiago, the capital of Chile. Arica has an infant mortality rate of 6.3 per 1000 born infants, and Santiago 6.9 per 1000 [27].

2.2. Exposure assessment

For evaluation of fetal exposure to lithium and boron in San Antonio de los Cobres, we used banked samples of arterial cord blood, placenta (only one available) and the first infant urine produced after birth collected from May to October 1996 for assessment of early-life arsenic exposure [28]. Maternal exposure was assessed from lithium and boron concentrations in drinking water, blood and urine and infant exposure through concentrations in breast-milk and urine (similarly banked samples). Spot-urine samples from both mothers and infants were used to estimate the lithium and boron exposure. Even though some studies have used 24-h urine to estimate the boron exposure [29], it has been shown that spot-urine samples can also be used as biomarkers of boron exposure in occupational and non-occupational populations [30,31]. Regarding lithium, we have previously shown that the concentrations in spot-urine samples correlated with the amount of drinking water consumed per day [6].

Eleven women in late gestation had been recruited at the antenatal center of the hospital in San Antonio de los Cobres. The maternal and infant samples were collected at delivery and at 2–4 weeks, 2–4 months, and 4–6 months after delivery/birth. Methods of collection of maternal and infant samples (infant urine collectors) and pre-analytical and analytical quality control have been previously described [28]. The used plastic containers for all types of samples were tested free from lithium and boron. All the samples have been kept at −20 °C. Infant weight and length were measured at birth.

In 2010, maternal blood, breast milk, and maternal and infant urine samples were collected in both Arica and Santiago, in relation to a project of the International Atomic Energy Agency aiming at evaluating exclusive breast-feeding in contaminated areas [32]. Maternal blood and urine, infant urine and breast milk samples were collected at 2–4 months after delivery/birth, in their homes. Maternal blood samples were separated into red blood cells (RBC) and plasma. Infant urine samples were collected using infant urine collectors. Breast milk samples were collected in plastic tubes by the midwife by gently compression of the breast, after careful cleaning of the skin. Also tap water samples from both cities were collected; both from the Health Care Centers where the subjects were recruited and close to the residence houses. All the samples were transported frozen to Sweden for analyses. Infant weight and length were also measured at birth.

In both, San Antonio de los Cobres, Arica, and Santiago, a questionnaire was fulfilled concerning maternal age, parity, years of residence and exclusive/non-exclusive breastfeeding.

Informed consent was obtained after oral explanation of the study. Ethical approvals were obtained from the Ethical Committee of the Institute of Nutrition and Food Technology (INTA), University of Chile (Chilean study), and from the Ministry of Health of Salta and the Karolinska Regional Ethics Committee (Argentinean study).

2.3. Sample preparation and analyses

Water and urine samples were diluted 1:10 with 1% nitric acid (Suprapur; Merck, Darmstadt, Germany) and then analyzed for lithium and boron using inductively coupled plasma mass spectrometry (ICPMS; Agilent 7500ce, Agilent Technologies, Tokyo, Japan) with collision/reaction cell in no gas mode [6]. As the samples from San Antonio de los Cobres had been stored in freezer for several years we tested the effects of storage on element concentrations by measuring the specific gravity (EUROMEX Model RD 712 clinical refractometer, Arnhem, Netherlands) [33] of the infant and maternal urine samples and comparing them with the data recorded in 1996. The specific gravity values measured in 2010 were higher by around 0.002 g/mL (mean specific gravity of all infants was 1.006 g/mL in 1996 and 1.008 g/mL in 2010; of all mothers 1.014 g/mL in 1996 and 1.015 g/mL in 2010), indicating that the samples had become somewhat more concentrated. However, because the samples of blood and breast milk probably also had dried to a similar extent, we considered the urine specific gravity values obtained in 2010. The lithium and boron concentrations in the collected urine samples were adjusted to the mean specific gravity of all three cohorts: 1006 g/mL for the infants and 1018 g/mL for the mothers.

Prior to analysis by ICP-MS, plasma, RBC, blood, cord blood, placenta and breast milk samples were digested. Approximately 0.5 g of each sample was mixed with 3 mL of deionized water and 2 mL of Nitric Acid (65% suprapur, Merck, Darmstadt, Germany) and digested at 250 °C for 30 min with a Milestone ultraCLAVE II microwave digestion system (EMLS, Leutkirch, Germany), as previously described for other elements [34]. After digestion, the samples were diluted with deionized water until 10.8 g of weight, to get a 20% nitric acid concentration. Concentrations of lithium and boron in breast milk expressed in μg/kg were converted into μg/L based on the specific gravity of mature breast milk (1.03 mg/L) [35].

For quality control, reference materials were digested together with the samples and analyzed after about every 15 samples. Because of the lack of certified standard reference materials (SRM), we used for blood, cord blood and RBC, reference samples from Seronorm (SERO AS, Billingstad, Norway): Seronorm$^{\text{TM}}$ Trace Elements Whole Blood LOT 0503109 Level 2; for breast milk and plasma, Serum Seronorm$^{\text{TM}}$ LOT NO0371y Level 2; and for urine, Seronorm$^{\text{TM}}$ Trace Elements Urine LOT NO2525 and Seronorm$^{\text{TM}}$ Trace Elements Urine Blank LOT OK4636, were used. For water samples, we used SRM 1643e Trace Elements in Water (National Institute of Standards and Technology (NIST), Gaithersburg, USA). In general, the obtained results agreed well with the reference values (Supplemental material, Table S1). The limits of detection (LOD) for blood were 0.18 μg/L Li and 2.0 μg/L B; for plasma, 0.14 μg/L Li and 1.3 μg/L B; for RBC and breast milk, 0.028 μg/L Li and 1.6 μg/L B; and for water and urine, 0.032 μg/L Li and 2.6 μg/L B. No samples had concentrations below the LOD values.

2.4. Statistical analysis

All the statistical analyses were performed using IBM® SPSS® Statistics 18.0 (SPSS, Chicago, IL, USA). Median, arithmetic and geometric mean (GM), standard deviation (SD) and range were calculated for all the continuous variables. Due to the small sample size and the variability in the results, GM was chosen for the concentrations of lithium and boron in the different media. To evaluate the transfer of the elements from the mother to the fetus and breast-milk, we calculated the ratios between concentrations in cord-blood or breast milk and those in maternal blood, as well as ratios between infant urine and breast milk. Spearman's rank correlations (r_s) were calculated to evaluate the associations between continuous variables. Mann–Whitney U and Kruskal–Wallis H tests were used to compare the differences between two or more independent groups, respectively. A p-value <0.05 was considered statistically significant.

3. Results

The main characteristics of the studied mothers and infants are shown in Table 1. Maternal age, parity and gestational week at birth were similar in the three areas. Birth weight and length were lower in San Antonio de los Cobres compared to Arica, but there were no statistically significant differences in birth weight and length between Santiago and the two other areas.

3.1. Lithium

The concentrations of lithium in maternal blood, cord blood, breast milk, maternal urine and infant urine in exclusively and non-exclusively breast-fed infants (from delivery/first day of birth to 6 months of age) in San Antonio de los Cobres are shown in Table 2. The concentrations of lithium in water, as well as maternal blood, plasma, RBC, urine, breast milk and infant urine from 2 to 4 months in the three study areas are presented in Table 3. In San Antonio de los Cobres, the GM lithium concentration in drinking water was about 700 μg/L, which was more than 10 times higher than that in Arica (60 μg/L) and Santiago (21 μg/L) (Table 3). The lithium concentrations in maternal urine in Arica and Santiago, collected 2–4 months after delivery, were about 10% of those in San Antonio de

Table 1
Characteristics of the study infants from San Antonio de los Cobres, Arica and Santiago.

Characteristics	San Antonio de los Cobres	Arica	Santiago
Mothers			
Number (N)	11	24	11
Age (years)[a]	28 (7)	25 (7)	30 (7)
Parity[b]	3 (1–9)	2 (1–6)	2 (1–5)
Years of residence (years)[a]	19 (13)	15 (8)	15 (11)
Infants			
Number (N)	11	24	11
Gestational week[a]	39 (2)	39 (1)	39 (1)
Birth weight (g)[a]	2966 (598)[c]	3498 (502)[c]	3303 (659)
Birth length (cm)[a]	48 (2.6)[c]	50 (2.4)[c]	49 (2.6)
Exclusive breastfeeding (yes/no)	8/3	17/7	8/3

[a] Mean value (standard deviation).
[b] Median and range.
[c] Values are significantly different between those areas ($p < 0.05$).

los Cobres (Table 3), similar to the differences in drinking water concentrations.

In San Antonio de los Cobres, the lithium concentrations in maternal blood were about 40 μg/L both at delivery and 2–4 weeks after delivery (Table 2), but significantly higher at 2 months after delivery (Table 2). Also, the lithium concentrations in maternal urine were similar at delivery and 2–4 weeks (about 1400 μg/L) and significantly higher 2 and 4 months after delivery (Table 2). Lithium concentrations in maternal blood and urine were highly correlated (Table 6). The lithium concentrations in cord blood (GM 70 μg/L, range 30–105; Table 2) were closely correlated with the concentrations in maternal blood ($r_s = 0.82$; $p < 0.01$; Table 6) in spite of the few samples available. The GM cord blood to maternal blood ratio for lithium was 1.5 (range 0.97–2.3). The lithium concentration in the placenta sample from San Antonio de los Cobres was 73 μg/kg wet weight. The concentrations in breast milk (2–4 months) also correlated with those in maternal blood (Table 6). In San Antonio de los Cobres the mothers provided breast milk samples several times over a period of about 6 months. In general, the lithium concentrations in breast milk 2–4 weeks after delivery (GM 23, range 8.8–53 μg/L) were similar to those collected at 2 months (GM 31, range 17–53 μg/L) and 4–6 months (GM 36, range 24–54 μg/L) (Table 2). Breast milk to blood/plasma ratios were similar (GM about 0.4) in the three cohorts, in spite of the marked differences in concentrations (Table 3).

The lithium concentrations in urine in breast-fed infants in San Antonio de los Cobres were more than 10 times higher than in Arica ($p < 0.001$) and Santiago ($p < 0.001$) (Table 3). The infant urine to breast-milk ratios of lithium in exclusively breast-fed infants were similar (on average 5) in the three cohorts. In San Antonio de los Cobres, the highest lithium concentrations in infant urine were found in the first urine produced after birth (GM 600 μg/L; Fig. 1 and Table 2). At 2 weeks of age, the urine concentrations in the exclusively breast-fed infants had decreased markedly (GM 120 μg/L; $p = 0.016$), being around 20% of the initial concentrations (Fig. 1 and Table 2). In the following months (4–6 months of age), the lithium concentrations in urine increased again (GM 380 μg/L; $p = 0.048$; Fig. 1 and Table 2) in parallel to the increasing concentrations in maternal blood and urine (Table 2). In San Antonio de los Cobres, the infants receiving formula based on milk powder and drinking water, had statistically significantly higher lithium concentrations in urine up to 4 months of age, than the exclusively breast-fed infants (Table 2), but in the older infants, the lithium urinary concentrations did not differed statistically. In Arica and Santiago, there were no statistically significant differences in infant

Table 2
Lithium concentrations in maternal blood, cord blood, breast milk, maternal urine, and infant urine, from delivery/first day of birth to 6 months in San Antonio de los Cobres, Argentina.

Concentrations of lithium	At delivery/first day of birth			2–4 weeks			2–4 months			4–6 months		
	N[a]	GM[b]	Range	N[a]	GM[b]	Range	N[a]	GM[b]	Range	N[a]	GM[b]	Range
Maternal blood (μg/L)	11	47	20–77	10	40	20–76	7	80[f]	36–160	7	88[e,f]	43–150
Cord blood (μg/L)	10	70	30–105	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]
Breast milk (μg/L)	–[d]	–[d]	–[d]	8	23	8.8–53	6	31	17–53	6	36	24–54
Maternal urine (μg/L)	11	1400	810–2300	10	1250	570–3600	8	3600[e,f]	1950–7000	8	2050[e,f]	860–3700
Infant urine (μg/L) (SG 1.006 g/mL)												
Exclusively breast-fed	7[c]	600[c]	140–1680[c]	5	120[e]	84–200	5	190	80–430	5	380[f]	175–725
Non-exclusively breast-fed	–[d]	–[d]	–[d]	2	41[g]	280–600	2	1130[g]	1035–1230	2	480	180–1150

[a] N: sample size.
[b] GM: geometric mean.
[c] Information is presented for both exclusively and non-exclusively breast-fed infants.
[d] Not applicable.
[e] Values are significantly different between this time-point and "at delivery/first day of birth" ($p < 0.05$).
[f] Values are significantly different between this time-point and "2–4 weeks" ($p < 0.05$).
[g] Values are significantly different between "exclusively" and "non-exclusively" breast-fed infants ($p < 0.05$).

Table 3
Concentrations of lithium in water, maternal red blood cells, plasma, serum, whole blood, urine, breast milk, and infant urine at 2–4 months of age, in San Antonio de los Cobres, Arica, and Santiago.

Concentrations of lithium	San Antonio de los Cobres			Arica			Santiago		
	N	GM[a]	Range	*N*	GM[a]	Range	*N*	GM[a]	Range
Water (μg/L)	4	705	650–740	9	60[f]	25–80	6	21[f,g]	16–34
Maternal blood[b]/plasma[c] (μg/L)	7	80[b]	36–160	24	11[c]	6.3–27	11	6.0[c]	4.1–8.0
Maternal red blood cells (μg/L)	–[d]	–[d]	–[d]	24	3.2	2.1–5.6	11	3.0	2.0–4.0
Breast milk (μg/L)	6	31	17–53	24	3.9[f]	2.0–8.3	11	2.7[f,g]	1.8–8.1
Maternal urine (μg/L)	8	3600	1950–7000	24	170[f]	90–290	11	57[f,g]	8.0–180
Infant urine (μg/L) (SG[e]: 1.006 g/mL)									
Exclusively breast-fed	5	190	80–430	17	17[f]	2.6–70	8	15[f]	4.0–80
Non-exclusively breast-fed	2	1130[h]	1030–1230	6	18[f]	7.0–50	3	18[f]	8.6–55

[a] GM: geometric mean.

[b] Whole blood from San Antonio de los Cobres.

[c] Plasma from Arica and Santiago.

[d] Not available data.

[e] SG: specific gravity.

[f] Values are significantly different between this exposure area and San Antonio de los Cobres ($p < 0.05$)

[g] Values are significantly different between this exposure area and Arica ($p < 0.05$).

[h] Values are significantly different between "exclusively" and "non-exclusively" breast-fed infants ($p < 0.05$).

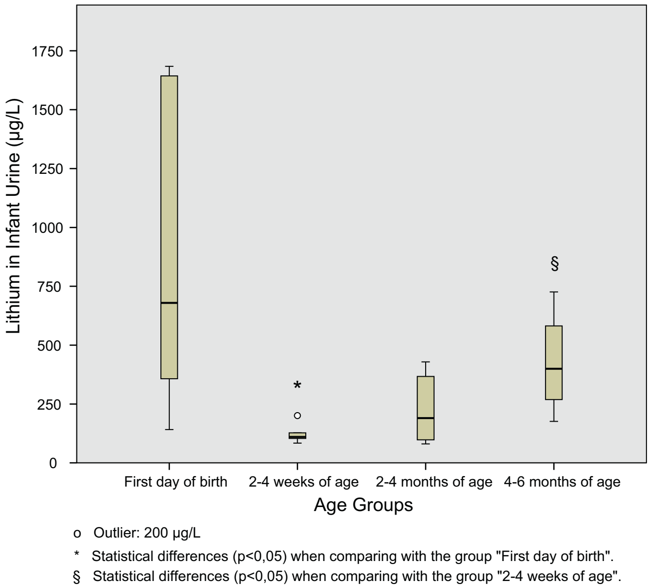


Fig. 1. Box plot of lithium concentrations in urine in exclusively breast-fed infants by age groups, in San Antonio de los Cobres.

urinary concentrations of lithium in relation to reported feeding practices.

3.2. Boron

The concentrations of boron in maternal blood, cord blood, breast milk, maternal urine and infant urine in exclusively and non-exclusively breast-fed infants, from delivery/first day of birth to 6 months from San Antonio de los Cobres are shown in Table 4. The concentrations of boron in water, maternal blood, plasma, RBC, urine, breast milk and infant urine from 2 to 4 months in the three study areas are presented in Table 5. The GM boron concentrations in drinking water were about 5000 μg/L in San Antonio de los Cobres and almost 8000 μg/L in Arica (Table 5), but only 187 μg/L in Santiago, the control area. In line with the water boron concentrations, the blood and urine concentrations in San Antonio de los Cobres and Arica were about 10 times higher than those in Santiago (Table 5), but there were marked inter-individual variations. Boron concentrations in RBC and plasma were highly correlated ($r_s = 0.99$; $p < 0.001$; Table 6). As was the case with lithium, the concentrations of boron in maternal blood in San Antonio de los Cobres were stable over the first 2–4 weeks after delivery (about 200 μg/L; Table 4), but increased to twice that level during the following months ($p = 0.003$; Table 4). Likewise, maternal urinary concentrations of boron at 2 months after delivery (GM 15,700 μg/L) were significantly higher than the first weeks postpartum (about 8000 μg/L; $p = 0.001$; Table 4).

The GM boron concentrations in cord blood were 145 μg/L (range 70–300; Table 4). The GM cord blood to maternal blood ratio for boron was 0.74 (range 0.27–1.2) with a correlation coefficient of 0.45 (San Antonio de los Cobres, Table 6). The boron concentration in the placenta sample from San Antonio de los Cobres was 222 μg/kg wet weight. The boron concentrations in breast milk at 2–4 months after delivery were similar in San Antonio and Arica (GM 250 and 270 μg/L, respectively; Table 5). The breast milk concentrations in Santiago (GM 38 μg/L; Table 5) were statistically significantly lower compared to San Antonio de los Cobres ($p = 0.001$) and Arica ($p < 0.001$) (Table 5). In all the study groups, the average breast milk to maternal blood ratio was 0.6–0.8.

As for lithium, the highest boron concentrations in infant urine were found in the first urine produced after birth (San Antonio

Table 4

Boron concentrations in maternal blood, cord blood, breast milk, maternal urine, and infant urine, from delivery/first day of birth to 6 months in San Antonio de los Cobres, Argentina.

Concentrations of boron	At delivery/first day of birth			2–4 weeks			2–4 months			4–6 months		
	N[a]	GM[b]	Range	*N*[a]	GM[b]	Range	*N*[a]	GM[b]	Range	*N*[a]	GM[b]	Range
Maternal blood (μg/L)	11	220	105–550	10	190	135–300	7	430[f]	210–1500	7	350[f]	165–1120
Cord blood (μg/L)	10	145	70–300	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]	–[d]
Breast milk (μg/L)	–[d]	–[d]	–[d]	8	160	83–280	6	255[f]	140–360	6	170	64–350
Maternal urine (μg/L)	11	8300	4800–13,200	10	7450	3400–12,600	8	15,700[e,f]	11,000–23,300	8	9700	3320–16,500
Infant urine (μg/L) (SG 1.006 g/mL)												
Exclusively breast-fed	7[c]	4170[c]	900–13,970[c]	5	920[e]	630–1450	5	885[e]	670–1580	5	1310	1130–1475
Non-exclusively breast-fed	–[d]	–[d]	–[d]	2	2075[g]	1830–2350	2	6560[g]	6530–6600	2	2620	1100–6100

[a] *N*: sample size.

[b] GM: geometric mean.

[c] Information is presented for both exclusively and non-exclusively breast-fed infants.

[d] Not applicable.

[e] Values are significantly different between this time-point and "at delivery/first day of birth" ($p < 0.05$).

[f] Values are significantly different between this time-point and "2–4 weeks" ($p < 0.05$).

[g] Values are significantly different between "exclusively" and "non-exclusively" breast-fed infants ($p < 0.05$).

Table 5

Concentrations of boron in water, maternal red blood cells, plasma, serum, whole blood, urine, breast milk, and infant urine at 2–4 months of age, in San Antonio de los Cobres, Arica, and Santiago.

Concentration of boron	San Antonio de los Cobres			Arica			Santiago		
	N	GM[a]	Range	*N*	GM[a]	Range	*N*	GM[a]	Range
Water (μg/L)	4	5200	4800–6000	9	7900[f]	4200–10,530	6	187[f,g]	150–260
Maternal blood[b]/plasma[c] (μg/L)	7	430[b]	210–1500	24	380[c]	125–1360	11	35[c]	21–66
Maternal red blood cells (μg/L)	–[d]	–[d]	–[d]	24	260	85–950	11	43	29–73
Breast milk (μg/L)	6	255	140–360	24	270	140–695	11	38[f,g]	18–180
Maternal urine (μg/L)	8	15,700	11,000–23,300	24	12,800	6300–25,000	11	1150[f,g]	190–3200
Infant urine (μg/L) (SG[e]: 1.008 g/cm^3)									
Exclusively breast-fed	5	885	670–1580	17	1320	250–6820	8	157[f,g]	47–600
Non-exclusively breast-fed	2	6560[h]	6530–6600	6	2150	450–6670	3	200[f,g]	144–350

[a] GM: geometric mean.

[b] Whole blood from San Antonio de los Cobres.

[c] Plasma from Arica and Santiago.

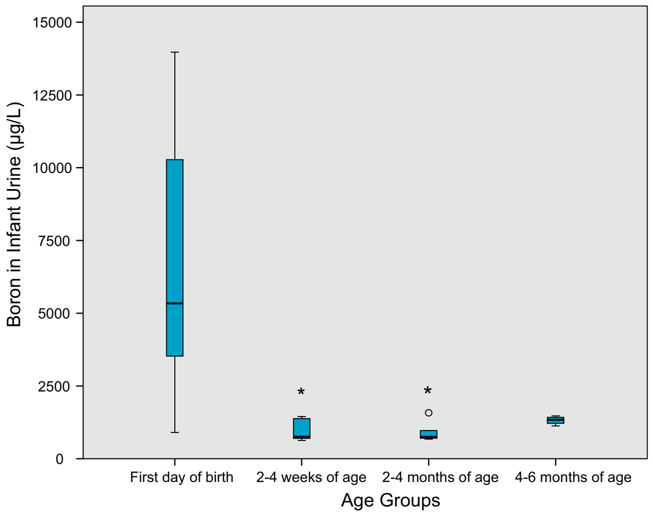
[d] Not available data.

[e] SG: specific gravity.

[f] Values are significantly different between this exposure area and San Antonio de los Cobres ($p < 0.05$).

[g] Values are significantly different between this exposure area and Arica ($p < 0.05$).

[h] Values are significantly different between "exclusively" and "non-exclusively" breast-fed infants ($p < 0.05$).



o Outlier: 1,580 μg/L

* Statistical differences (p<0,05) when comparing with the group "First day of birth".

Fig. 2. Box plot of boron concentrations in urine in exclusively breast-fed infants by age groups, in San Antonio de los Cobres.

de los Cobres, GM 4170 μg/L), with a wide variation (range 900–13,970 μg/L; Table 4 and Fig. 2). In the exclusively breast-fed infants, the concentrations then decreased markedly (GM 920 μg/L, $p = 0.028$; Table 4), being around 25% of the initial concentrations during the first months in life. In infants receiving formula, the urine concentrations of boron during the first months in life (up to 6500 μg/L; Table 4) were significantly higher compared to non-exclusively breast-fed infants (up to 1580 μg/L; Table 4). These differences were statistically significant only in the infants up to 4 months of age ($p < 0.05$ at both 2–4 weeks and 2–4 months of age). After this age, the urinary concentrations of boron in relation to feeding practice did not differed statistically. In Arica and Santiago, there were no statistically significant differences in urinary concentrations of boron in relation to reported feeding practice. The infant urine to breast milk ratio in the exclusively breast-fed infants was similar (about 4.0) in all the three cohorts.

Concentrations of lithium and boron were highly inter-correlated in urine (maternal and infant urine) and blood, while the correlation in breast milk was weaker (Table 6).

4. Discussion

To the best of our knowledge this is the first study to show that consumption of drinking water with elevated concentrations of lithium and boron during pregnancy causes exposure of the fetus. Infant exposure to lithium and boron through breast milk was markedly lower than the prenatal exposure.

In spite of the few mother–newborn pairs studied, which is a major draw-back of the study, the results show clearly that the cord blood concentrations of lithium were highly correlated with the maternal blood concentrations. The GM concentration of lithium in cord blood found in this study (70 μg/L) is more than 100 times higher than the reference value for lithium in cord serum suggested by Alimonti et al. (0.58 μg/L) [36]. Cord blood to maternal plasma ratios (between 0.75 and 1.2) were similar as those reported for mothers receiving lithium doses between 300 and 1800 mg/day as therapy for bipolar disease [15], i.e. about three orders of magnitude higher than in the present study, indicating no saturation effects. These results indicated a similar free passage of lithium through the placenta as previously reported for medical lithium [17,37]. The previously observed elevated lithium concentrations in the amniotic fluid of mothers on lithium therapy [16] show that the highly elevated concentrations found in the first infant urine after birth in the high-exposure area (Table 2) is a result of a continuous fetal oral exposure through the amniotic fluid, rather than an accumulation in the fetal tissues. Possibly, this was also the case for boron. The transfer of boron to the fetus, which as far as we know is studied for the first time, seemed to be only slightly lower than that of lithium.

There are very few data on lithium and boron concentrations in placenta. A study in rabbits showed a background placental lithium concentration of 3.6 μg/L (one sample) at delivery [38], while the placenta from one mother from San Antonio de los Cobres in the present study had 20 times higher concentration (73 μg/kg). Two mechanisms of placental transfer of lithium have been suggested: bidirectional diffusion and fetal–maternal unidirectional active transport were Na^+/K^- ATPase might be involved [38]. The boron concentration in the placenta of the present study (222 μg/kg wet weight) was almost three times higher than the proposed threshold value for impairment of δ-aminolevulinic acid dehydratase (ALA-D) function [39]. Huel et al. showed a negative association of boron in placental tissue ($N = 197$) from French mothers with the activity of ALA-D in cord blood and suggested a threshold value of 80 μg/kg in placenta [39].

After the first urine produced in life, the concentrations of lithium and boron in infant urine decreased. The concentrations in infant urine collected at 2–4 weeks of age were only about 20% of that in the first urine, reflecting a lower exposure during exclusive breast-feeding. However, after 4 months, the concentrations in infant urine, particularly of lithium, increased again, possibly due to an increased intake of breast milk at this age in the exclusively breast-fed infants [40]. However, we cannot exclude that the infants were given some supplemental food also at this age. Interestingly, there was a similar trend of increasing concentrations in maternal blood and urine as well (Tables 2 and 4). Probably, this was due to an increased intake of water in the mothers during lactation [41]. The samples of this time-point were all collected during one week in August 1996, which might represent higher concentrations of lithium and boron in the drinking water in this particular period. The few available data on concentrations of lithium and boron in drinking water do indicate geographic and seasonal variations [4–9,42,43]. However, analysis of lithium and boron in stored samples collected in San Antonio de los Cobres during 1994–2005 (mostly March–November) showed that the concentrations were fairly stable over time (Mean ± SD 677 ± 32 μg/L for lithium and 4680 ± 198 μg/L for boron; $N = 7$; unpublished data). The highest concentrations of lithium and boron was found in water collected in December 2008 [6], one of the driest months of the year, but there were no indications of higher concentrations during the winter (including august). Seasonal variation has been shown for lithium in Czech Republic and for boron in Turkey [42,43].

While the exclusively breast-fed infants had significantly lower urinary concentrations of lithium and boron at 0.5–4 months of age than the non-exclusively breast-fed infants in San Antonio de los Cobres no such difference was found after 4 months of age, probably due to the introduction of water or additional food in the breast-fed infants. The questionnaire about breast-feeding used in the present study was completed only at the beginning of the breastfeeding period, thus, we had no data on breastfeeding practices for the older infants. Infants in Arica and Santiago showed no differences in the urinary concentrations of lithium and boron in relation to breastfeeding. This might be due to a misunderstanding of the terms exclusively and non-exclusively breastfeeding when answering the questionnaire, rather than an actual lack of difference in the exposure between these two groups. This was apparently not the case in San Antonio de los Cobres, where promotion of breastfeeding is continuously performed by the

Table 6
Spearman's correlation coefficients between lithium and boron concentrations in the different samples collected at birth (maternal/cord blood) and at 2–4 months post-partum, in San Antonio de los Cobres, Arica, and Santiago.

Area/media	Lithium					Boron					
	Maternal plasma	Maternal urine	Breast milk	Cord blood	Infant urine	Maternal RBC	Maternal blood/plasma	Maternal urine	Breast milk	Cord blood	Infant urine
San Antonio de los Cobres											
Lithium											
N	0	7	7	10	10	0	7	7	7	10	10
Maternal blood		0.93[a]	0.80	0.82[a,c]	0.75[b,c]	–[d]	0.75[b]	0.96[a]	0.99[a]	0.77[a,c]	0.71[c]
Maternal urine			0.89[b]	–[d]	0.54[e]	–[d]	0.64	0.91[a]	0.99[a]	–[d]	0.54[b,e]
Breast milk				–[d]	0.55[f]	–[d]	0.30	0.89[b]	0.89[b]	–[d]	0.36[f]
Cord blood					0.46[c]	–[d]	0.19[c]	−0.13	–[d]	0.88[a,c]	0.48[c]
Infant urine							−0.07[c]	0.14[e]	0.13[f]	0.48[c]	0.95[a]
Boron											
Maternal blood								0.71	0.60[b]	0.45[c]	0.01[c]
Maternal urine									0.99[a]	0.079[c]	0.46[e]
Breast milk										–[d]	0.08[f]
Cord blood											0.71[c]
Arica											
Lithium											
N	24	24	24	0	23	24	24	24	24	0	23
Maternal RBC[g]	0.86[a]	0.24	0.47[b]	–[d]	–[d]	0.77[a]	0.77[a]	0.31	0.70[a]	–[d]	–[d]
Maternal plasma		0.26	0.47[b]	–[d]	–[d]	0.77[a]	0.77[a]	0.31	0.57[a]	–[d]	–[d]
Maternal urine			0.20	–[d]	0.49[e]	0.11	0.11	0.76[a]	0.44[b]	–[d]	0.77[a,e]
Breast milk					0.47[b,f]	0.47[b]	0.47[b]	0.29	0.56[a]	–[d]	0.48[b,f]
Infant urine						–[d]	–[d]	0.71[a,e]	0.41[b,f]	–[d]	0.85[a]
Boron											
Maternal RBC							0.99[a]	0.43[b]	0.59[a]	–[d]	–[d]
Maternal plasma								0.44[b]	0.60[a]	–[d]	–[d]
Maternal urine									0.57[a]	–[d]	0.95[a,e]
Breast milk											0.62[a,f]
Santiago											
Lithium											
N	11	11	11	0	10	11	11	11	11	0	10
Maternal RBC	0.40	0.75[b]	0.25	–[d]	–[d]	0.75[a]	0.84[a]	0.75[b]	0.24	–[d]	–[d]
Maternal plasma		0.75[b]	0.39	–[d]	–[d]	0.51	0.54	0.71	−0.50	–[d]	–[d]
Maternal urine			0.07	–[d]	−0.50[e]	0.61	0.71	0.90[a]	0.43	–[d]	−0.50[e]
Breast milk					−0.38[f]	0.0046	0.35	0.32	0.19	–[d]	−0.65[f]
Infant urine						–[d]	–[d]	0.71[e]	0.64[f]	–[d]	0.92[a]
Boron											
Maternal RBC							0.67[b]	0.79[b]	0.79[b]	–[d]	–[d]
Maternal plasma								0.86[b]	0.86[a]	–[d]	–[d]
Maternal urine									0.64	–[d]	−0.50[e]
Breast milk											0.45[f]

[a] $p < 0.01$.
[b] $p < 0.05$.
[c] At birth/delivery.
[d] Not available data/not applicable.
[e] Non-exclusively breast-fed infants.
[f] Exclusively breast-fed infants.
[g] RBC: red blood cells.

hospital personnel and thus, the definition of exclusively and non-exclusively breastfeeding is better understood.

Lithium and boron concentrations in breast milk collected at 2–4 months post-partum (GM values about 30 and 200 μg/L, respectively, in San Antonio de los Cobres; about 4 and 280 μg/L, in Arica; and about 3 and 40 μg/L in Santiago) represented on average 35–60% of the lithium concentrations in blood or plasma and 60–100% of the blood boron concentrations. Thus, there were wide variations between mothers. A similar variation in the blood to plasma ratio of lithium has been reported for mothers receiving lithium therapy (milk concentrations constituting 10–80% of maternal blood concentrations) [17–19], suggesting that there is an inter-individual variation in the transfer of lithium through the mammary gland. This might, at least partly be due to the short half-life of lithium in the plasma [44], but also additional factors, i.e. transcellular mechanisms or content of essential trace elements in breast milk, might influence this transfer [38,45]. Lithium concentrations of 700–3500 μg/L have been observed in breast milk of mothers on lithium therapy [18], i.e. much higher than the concentrations found in the mothers in the present study. Certain studies have recommended avoiding breast-feeding during lithium therapy [17,37], but this is not a universal recommendation [46]. On the contrary, in the case of exposure through drinking water breast-feeding protects the infant from the excessive exposure via drinking water.

There are very few data on boron in breast milk. Concentrations between 250 and 300 μg/L were found in a study on trace elements in breast milk in Missouri, USA [22], i.e. similar to those in the presently study women from San Antonio de los Cobres and Arica with more than 5000 μg/L in the drinking water. The sources of the exposure in the Missouri study are not known. Much lower boron concentrations in breast milk, 10–60 μg/L, were recently found in Canadian mothers [21], i.e. similar to the ones in the control group of the present study. Probably, these concentrations reflect the "background" exposure through drinking water and food.

Lithium and boron concentrations were highly inter-correlated in most of the media of this study, probably due to similar kinetics [37,47]. Both elements are rapidly absorbed through the gastrointestinal tract and have a fast excretion through the kidneys. However, the mechanisms of transfer to the different tissues and organs might be different [37,47]. The lithium transport across the erythrocyte plasma membrane is reported to be mediated by the Na^+–Li^+ counter or exchange transporter [48]. We found a very high correlation between plasma and RBC concentrations of both lithium and boron ($r_s = 0.86$; $p < 0.001$, and $r_s = 0.99$; $p < 0.001$; respectively).

Lithium and boron in breast milk showed slightly lower correlation than in other media, probably related to the differences in the blood to breast milk transfer (twice as high for boron as for lithium). The reason for this is not known. For adults, the half-life of both lithium and boron in the body is about 1–2 days [12,44]. In the present study, the lithium and boron concentrations in urine of the infants just after birth were around 8 times higher (range 5–16 times) and 28 times higher (13–46 times), respectively, than those in cord blood, suggesting a high clearance also in infants. The amiloride-sensitive epithelial sodium channel (ENaC) has been suggested as candidate transporter for the uptake of lithium in the kidney collecting duct [49]. However, this may be less developed during infancy, as both glomerular and tubular functions continue to develop during infancy [50]. Therefore, there may be a low degree of reabsorption in the proximal tubule of the circulating lithium filtered into the primary urine. The inability of the immature infant kidney to concentrate the primary urine in the renal tubule was apparent from the low specific gravity of the infant urine (average 1006 g/mL), compared to the mothers (1018 g/mL).

As mentioned above, health consequences of early-life exposure to lithium have previously only been studied in relation to maternal lithium therapy for mental diseases [15,17,18,51,52]. However, we recently found negative effects on thyroid function in women exposed to lithium through drinking water in San Antonio de los Cobres [53]. During pregnancy, such an effect may have unfavorable consequences for fetal development, as shown for other anti-thyroid chemicals [54].

Even less is known about the potential negative effects of elevated water boron concentrations during pregnancy. A few experimental studies have shown low birth weight, malformations in thoracic and lumbar ribs and brain, and kidney lesions in rats, mice and rabbits. [20,55]. Based on those findings, Fail et al. suggested a NOAEL of 9.6 mg B/kg bw/day for rats and mice and 22 mg B/kg bw/day for rabbits [20]. In the present study, water boron concentrations could exceed 10 mg/L in Arica, suggesting an exposure of about 3 mg/kg bw/day in a 3 kg formula-fed infant. This value is much higher (17 times) than the recommended TDI (Total Daily Intake: 0.2 mg/kg bw) [12] and just slightly lower than the NOAEL. It should be noted, though, that the studied women in Arica, with boron concentrations in drinking water of around 8 mg/L, had infants with the largest size at birth and similar mortality rate as in Santiago. Obviously, more studies are needed to understand the mechanisms and susceptibility factors of boron toxicity in early life.

5. Conclusions

This is the first study assessing early-life exposure to lithium and boron in relation to elevated concentrations in drinking water. Both elements seem to pass easily through the placenta, and potential health effects need to be evaluated. Exclusively breast-fed infants seem to have a lower exposure than the formula-fed infants. Against the background of very few data on these elements in drinking water, more regular monitoring is warranted.

Conflict of interest

No conflicts of interest are to be declared.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.reprotox.2012.08.009.

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