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High concentrations of essential and toxic elements in infant formula and infant foods – A matter of concern

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ABSTRACT

This study assessed concentrations in and intake of toxic and essential elements from formulas and foods intended for infants during their first 6 months of life. Concentrations of the essential elements Ca, Fe, Zn, Mn and Mo were significantly higher in most formulas than in breast milk. Daily intake of Mn from formula varies from ten up to several hundred times the intake of the breast fed infant, levels that may be associated with adverse health effects. One portion of infant food provided significantly more Fe, Mn, Mo, As, Cd, Pb and U than one feeding of breast milk, but less Ca, Cu and Se. Rice-based products in particular contained elevated As concentrations. Drinking water used to mix powdered formula may add significantly to the concentrations in the ready-made products. Evaluation of potentially adverse effects of the elevated element concentrations in infant formulas and foods are warranted.

1. Introduction

Breast milk is recommended as the sole source of infant nutrition for the first 6 months of life. However, less than 35% of the world's infants are exclusively breast fed at this age (WHO, 2009). While less than 40% of 6 month old infants are exclusively breast fed in developing countries (WHO, 2009), only 13% of US infants and 3% of European infants are exclusively breast fed at this age (CDC, 2010; Freeman, van't Hof, & Haschke, 2000). Substitutes to breast milk include other milks, sweetened liquids and solid foods in the developing world (Marriott, Campbell, Hirsch, & Wilson, 2007), while infant formula is the most common substitute in the US and in Europe for infants younger than 4 months (Freeman, van't Hof, & Haschke, 2000; Grummer-Strawn, Scanlon, & Fein, 2008). In addition to formula, a number of commercial infant foods are available, intended for consumption before the age of 6 months. Approximately two thirds of European infants are reportedly fed some solid foods at 4 months of age (Freeman, van't Hof, & Haschke, 2000). Although the EU limits infant food products to be marketed towards infants younger than 4 months (European Commission, 2006), a study on feeding patterns in 12 countries across Europe reported that complementary foods, most often fruits, vegetables or cereals, were in some countries first introduced to infants as early as 1 month of age (Freeman et al., 2000). Sweden has one of the highest rates of breast feeding in Europe with 12% exclusively breast fed at 6 months, but breast feeding has declined in recent years and the use of substitutes is increasing (Socialstyrelsen, 2009, 2010).

Substitutes to breast milk must provide sufficient supplies of energy and nutrients to support the rapid growth rate during the infant's first 6 months of life. Inadequate or incorrect nutrient and energy intakes can directly affect infant growth and can have long-term consequences on organ development and function, which may result in adverse health effects later in life (SCF, 2003). Recent research on formula composition has focused mainly on protein and energy content and a few nutrients and vitamins (Agostoni & Domellof, 2005). Most essential trace elements present in infant formula have received very little attention. For example, for eight out of the eleven essential elements regulated in formula, the data required for a science-based risk assessment of infant exposure is currently lacking (Codex Alimentarius Commission, 2007). Moreover, infant formula and foods may hold toxic elements as a result of their natural presence in raw materials used, from contamination, or from food processing. For example, rice-based food products intended for children were recently reported to contain concentrations of arsenic above what is considered safe (Meharg et al., 2008). In order to increase the knowledge on infant exposure to trace elements, we have assessed the concentrations of a range of essential and toxic elements in infant formulas and infant foods intended for consumption during the first 6 months of life. We have also calculated intakes from formula and food in relation to intakes of the exclusively breast fed infant.

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2. Materials and method

2.1. General

Nine infant formulas and nine infant foods purchased in Sweden were analysed for trace element concentrations. The infant formulas are intended for consumption from birth and the infant foods from 4 months of age. Most products are available worldwide and are produced by the major manufacturers of infant formulas and infant foods (Mead Johnson, Semper, Nestlé, Holle, Vitagermine, Hipp, Organix). All products were in powdered form and prepared with the ratio of powder to liquid given by the manufacturers. Although some foods were intended for mixing with formula, all formulas and all foods were prepared in duplicate with deionised water at temperatures given by the manufacturers. The formulas were prepared in 130 ml polycarbonate baby bottles (Esska) and infant foods in 170 ml plastic (SAN) containers.

All prepared formulas and foods were digested in duplicate using a Milestone ultraCLAVE II microwave digestion system (EMLS, Leutkirch, Germany). Samples (~1 g) were mixed with 2 ml of nitric acid (65% suprapur, Merck, Darmstadt, Germany) and 3 ml of deionised water, and thereafter heated at 250 °C for 30 min in the ultraCLAVE. Digested samples were transferred to acid-washed polyethylene tubes (SARSTEDT, Nümbrecht, Germany) and diluted with deionised water to a nitric acid concentration of 20%. The obtained solutions were measured for the essential elements calcium (Ca), magnesium (Mg), iron (Fe), zinc (Zn), copper (Cu), manganese (Mn), molybdenum (Mo) and selenium (Se), as well as the toxic elements arsenic (As), cadmium (Cd), antimony (Sb), lead (Pb) and uranium (U), using inductively coupled plasma mass spectrometry (ICPMS; Agilent 7500ce Agilent Technologies, Waldbronn, Germany) with a collision/reaction cell system. Mg, Ca, Mn, Fe, Cu, Zn, Mo, As and Cd were measured in helium mode, Se in hydrogen mode and Sb, Pb and U in standard mode. Analytical quality control included analysis of certified reference materials (Infant/Adult Nutritional Formula, NIST 1849, National Institute of Standards and Technology, Gaithersburg, MD; Seronorm™ Trace Elements Whole Blood L-1, REF 201505, LOT MR4206, SERO AS, Billingstad, Norway and; Seronorm™ Trace Elements Whole Blood L-2, REF 201605, LOT 0503109, SERO AS, Billingstad, Norway). The obtained results generally agreed with the recommended reference values. Two baby bottles and two food containers (bowls) were prepared with only deionised water to provide sample blanks. Bottle and bowl blanks held <0.1% of the average sample concentrations for Mg, Mn, Fe, Cu, Zn, Se, Mo and U, <0.5% for Ca and As and <1% for Cd and Sb. Blank values of Pb were found at 5.5% and 3.4% of the average formula and food concentrations, respectively. The blank Pb values were subtracted from the obtained formula and food concentrations. All sample preparation and analyses were carried out at the Unit of Metals and Health, Institute of Environmental Medicine, Karolinska Institutet, Sweden.

2.2. Calculations

One millilitre of the prepared infant formula was weighed repeatedly for determination of density in order to calculate concentrations in μg/l. The densities ranged from 1.02 to 1.04 kg/l. Significant differences in distribution of elemental concentrations between groups of formula/food were tested using the non-parametric Kruskal–Wallis test (Kruskal & Wallis, 1952). The significance of differences in formula concentrations compared to breast milk concentrations was tested using Student's *t*-test.

2.2.1. Intake from breast milk

There is no recent data on breast milk concentrations of the investigated elements in Swedish women. WHO (1989) provides data on Swedish breast milk concentrations of all elements investigated in the present study except U at 3 months lactation ($n = 86$). However, Hallén, Jorhem, Lagerkvist, and Oskarsson (1995) provide more recent data on Cd and Pb in Swedish women at week 6 of lactation ($n = 35$) while Wappelhorst, Kuhn, Heidenreich, and Markert (2002) have measured U concentrations in breast milk of German, Polish and Czech mothers ($n = 19$) at 2–8 weeks lactation. These more recent data were used instead of the WHO data. Wappelhorst et al. (2002) also measured Sb and found much lower concentrations than what was found in the WHO study. No other studies on Sb in breast milk were found. Due to the possible problems of contamination, or higher levels of environmental exposure in 1989 than in 2002, the Sb results from Wappelhorst et al. (2002) were used. These breast milk concentrations from the literature were used together with a daily milk intake of 702 g (Sievers, Oldigs, Santer, & Schaub, 2002) for the exclusively breast fed infant in order to calculate daily element intakes from breast milk. Although the breast milk concentrations from the literature were at 3 months lactation, they were assumed to represent relatively well the concentrations at 6 weeks as most trace element concentrations decrease with duration of lactation but tend to stabilise after the first few weeks (Perrone, Di Palma, Di Toro, Gialanella, & Moro, 1993). Intake of the investigated elements from one portion of breast milk as well as daily intake at 4 months of age were calculated using the same breast milk concentrations as above and the median milk intake per feed (portion) of 140 and 800 g per day for the exclusively breast fed infant at 17 weeks (4.25 months) as provided by Sievers et al. (2002). Similar to the rationale above, breast milk concentrations at 2–8, 6 weeks and 3 months lactation were assumed to relatively well represent concentrations at 17 weeks, as concentrations in breast milk vary little after the first month of lactation.

2.2.2. Intake from formula

Feeding patterns differ between formula and breast fed infants, with higher milk intakes in formula fed infants from the sixth week of life (Sievers et al., 2002). Daily intake of elements from formula was calculated using the obtained concentrations and data on milk intakes from Sievers et al. (2002) for formula fed infants at 6 weeks of age (837 g). Daily element intakes and intake from one portion of formula at 4 months were calculated using the obtained concentrations and intakes of 1006 (daily) and 200 g (portion) (Sievers et al., 2002).

2.2.3. Intake from infant food

Element intake from one portion of infant food at 4 months of age was calculated using the obtained concentrations and the portion serving size recommended by the manufacturers (67–225 g per portion). Although authorities recommend exclusive breast feeding up to 6 months age, parents do not always follow the set guidelines. Globally, it is estimated that 85% of mothers do not comply with these recommendations (Synnott et al., 2007). Briefel, Reidy, Karwe, and Devaney (2004) reported that around 30% of US infants were introduced to infant cereals or pureed food before the age of 4 months, and only 6% after 6 months. The mean age of introducing cereals to infants was 4.2 months. In Sweden, the National Food Board recommends the introduction of taste portions (0.5–1 teaspoon) around 4–6 months of age (Livsmedelsverket, 2002), but Swedish parent internet forums reveal that many infants receive full food portions at this age (e.g. www.familjeliv.se, www.viforaldrar.se). According to these forums, it seems common to substitute 2–3 portions of formula or breast milk with two meals of porridge, puree or mash between 4 and 6 months of age. Daily element intake from both food and formula at 4 months were calculated based on the assumption that two meals of formula are substituted with two meals of food at this age. The range of possible daily intakes was calculated by adding the daily intake of two meals of each food with the minimum, median and maximum intake of each element from three meals of formula per day, as intakes will vary depending on which formula is used.

3. Results

3.1. Infant formula

Concentrations of the investigated elements in the nine analysed ready-to-eat formulas are presented in Table 1. The concentrations are presented as means ± SD of the four measurements for each formula. All formulas were fortified by the manufacturers with Ca, Cu, Fe and Zn, five with Mn, one with Mo and six with Se. Concentrations of Ca, Mg, Fe, Zn, Cu, Se and Pb generally varied little between formulas, while large differences were found for Mn, Mo and the toxic elements As, Cd, Sb and U. The soy based formula held among the highest concentrations of all elements except Mn, Mo and Se. The hypoallergenic formulas held significantly higher concentrations of Mn, Sb and U than the conventional formulas ($p < 0.05$), while the organic milk based formulas held lower concentrations of Se, Cd and U, and higher concentrations of Ca, Fe and Mo than the non-organic cow's milk formulas.

Table 1 also presents concentrations of the investigated elements in breast milk, as reported in the literature (Hallén et al., 1995; Wappelhorst et al., 2002; WHO, 1989). Concentrations of all investigated elements except Mo, Cd, Sb and Pb seem to vary little in breast milk. The concentrations of all measured essential elements except Mg, Cu and Se were significantly higher in all investigated formulas than in breast milk ($p < 0.05$). Most infant formulas held around 2-fold the concentrations of Ca compared to breast milk. Concentrations of Zn were 5–10-fold the average concentrations in breast milk, Fe 10–35-fold and Mo 15–90-fold. The three milk-based infant formulas that were not fortified with Mn held around 10-fold the Mn concentration of breast milk, while the fortified formulas held up to 150 times more Mn than what is found in breast milk. One formula had a similar Mg concentration as breast milk while the remaining had significantly higher concentrations ($p < 0.05$). Similarly, one formula had lower Cu concentration than breast milk while the remaining formulas were significantly higher ($p < 0.05$) in spite of all formulas being fortified with Cu. Five formulas held higher Se concentrations than breast milk, two held similar Se concentrations and two held around half the Se concentration of breast milk. All infant formulas but one held higher concentrations of Cd (1.3–20 times), Pb (1.6–3 times) and U (1.7–46 times) than the average breast milk concentrations, while three formulas had 2–3 times higher As concentrations than breast milk. Four formulas had lower Sb concentrations than breast milk and the five hypoallergenic formulas had higher concentrations (1.3–5.6 times).

Table 2 shows the calculated daily intakes of the investigated elements in exclusively breast fed infants (daily milk intake 702 g) and in infants given only formula (daily milk intake 837 g), all at 6 weeks of age. The calculations show that the formula fed infant would have a higher intake of all elements but Se than the breast fed infant as a result of both higher concentrations in formula and higher daily milk intake. The intake of Se would be similar to that of the breast fed infant from all formulas but two (organic milk products), which would provide less than half of the daily Se intake from breast milk. Exclusive formula feeding would result in 2–3 times higher intake of Ca, Mg and Cu than the exclusively breast fed infant, while intake of Zn, Fe, Mo and Mn in formula would result in daily intakes of up to 12-, 44-, 114- and 190-fold the intake of the exclusively breast

Table 1
Concentrations of essential and toxic elements in infant formulas (mean ± SD) and in breast milk from Swedish mothers at 3 months lactation for Ca, Mg, Fe, Zn, Cu, Mn, Mo, Se, and As (mean ± SD) (WHO, 1989), at 6 weeks lactation for Pb and Cd (mean ± SD) (Hallén et al., 1995) and at 2–8 weeks lactation for Sb and U (median(min–max)) (Wappelhorst et al., 2002). Milk = cow's milk.

	Breast milk	Organic milk	Organic milk	Milk	Milk	Milk, partly hydrolysed[a]	Casein, extensively hydrolysed[a]	Whey, extensively hydrolysed[a]	Milk, rice starch[a]	Soy protein[a]
Essential elements										
Ca mg/l	250 ± 10[c]	567 ± 32[b]	549 ± 14[b]	435 ± 6.1[b]	416 ± 7.0[b]	379 ± 5.8[b]	531 ± 84[b]	489 ± 64[b]	533 ± 10[b]	641 ± 84[b]
Mg mg/l	37 ± 1.8[c]	66 ± 3.9[b]	50 ± 1.4	57 ± 0.86[b]	36 ± 0.64[b]	70 ± 0.68[b]	70 ± 0.28[b]	48 ± 6.2	49 ± 1.4	73 ± 10[b]
Fe mg/l	0.3 ± 0.02[c]	7.8 ± 0.37[b]	4.4 ± 0.10[b]	3.6 ± 0.03[b]	3.5 ± 0.03[b]	5.7 ± 0.07[b]	9.1 ± 0.22[b]	5.8 ± 0.68[b]	6.4 ± 0.2[b]	9.1 ± 1.3[b]
Zn mg/l	0.8 ± 0.05[c]	6.1 ± 0.31[b]	4.7 ± 0.10[b]	5.1 ± 0.04[b]	3.7 ± 0.14[b]	6.4 ± 0.08[b]	4.7 ± 0.03[b]	5.0 ± 0.62[b]	6.4 ± 0.1[b]	7.4 ± 1.0[b]
Cu µg/l	250 ± 15[c]	417 ± 22[b]	164 ± 3.2[b]	343 ± 3[b]	327 ± 6.7[b]	446 ± 6.2[b]	388 ± 12[b]	323 ± 38[b]	429 ± 37[b]	474 ± 22[b]
Mn µg/l	3.2 ± 0.27[c]	32 ± 1.7	25 ± 0.58	188 ± 2[b]	25 ± 0.44	141 ± 1.8[b]	499 ± 3.9[b]	394 ± 50[b]	363 ± 7[b]	367 ± 46
Mo µg/l	0.4 ± 0.32[c]	22 ± 1.2	24 ± 0.72	6 ± 0.1	18 ± 5.1	19 ± 0.33	37 ± 4.3[b]	37 ± 0.49	18 ± 0.5	21 ± 2.8
Se µg/l	13 ± 0.9[c]	5.9 ± 0.28	5.7 ± 0.11	16 ± 0.5[b]	18 ± 0.36[b]	29 ± 0.24	18 ± 1.1[b]	13 ± 1.9[b]	15 ± 0.4[b]	15 ± 2[b]
Toxic elements										
As µg/l	0.6 ± 0.15[c]	0.55 ± 0.03	0.60 ± 0.04	0.76 ± 0.03	0.17 ± 0.03	0.33 ± 0.07	0.98 ± 0.06	1.18 ± 0.18	0.41 ± 0.03	1.58 ± 0.21
Cd µg/l	0.06 ± 0.04[d]	0.12 ± 0.03	0.08 ± 0.02	0.39 ± 0.08	0.35 ± 0.01	0.29 ± 0.02	0.33 ± 0.13	0.13 ± 0.03	0.14 ± 0.01	1.17 ± 0.15
Sb µg/l	0.12(0.06–5.6)[e]	0.09 ± 0.01	0.09 ± 0.06	0.07 ± 0.01	0.03 ± 0.00	0.26 ± 0.01	0.50 ± 0.05	0.26 ± 0.03	0.16 ± 0.01	0.68 ± 0.08
Pb µg/l	0.5 ± 0.3[d]	1.3 ± 0.04	1.05 ± 0.07	1.16 ± 0.11	0.85 ± 0.02	0.82 ± 0.10	1.42 ± 0.04	0.99 ± 0.18	1.42 ± 0.13	1.50 ± 0.04
U µg/l	0.03(0.01–0.11)[e]	0.09 ± 0.01	0.05 ± 0.00	0.35 ± 0.04	0.17 ± 0.01	0.82 ± 0.01	0.74 ± 0.01	1.39 ± 0.19	0.78 ± 0.03	1.38 ± 0.16

[a] Hypoallergenic formulas for special medical purposes.
[b] Fortified.
[c] Mean ± SD, $n = 86$ (WHO, 1989).
[d] Mean ± SD, $n = 35$, 6 weeks (Hallén et al., 1995).
[e] Mean(min–max), $n = 19$ (Wappelhorst et al., 2002).

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Table 2
Daily median intakes of Ca, Mg, Fe, Zn, Cu, Mn, Mo, Se, As, Cd, Sb, Pb and U from formula and from exclusive breast feeding at 6 weeks of age.

	Breast milk	Organic milk	Organic milk	Milk	Milk	[a]Milk, partly hydrolysed	[a]Casein, extensively hydrolysed	[a]Whey, extensively hydrolysed	[a]Milk, rice starch	[a]Soy protein
Essential elements										
Ca mg	176	492[b]	479[b]	376[b]	360[b]	328[b]	460[b]	420[b]	459[b]	558[b]
Mg mg	26	57[b]	44[b]	49[b]	31	61[b]	61	41[b]	42	64[b]
Fe mg	0.18	6.8[b]	3.8[b]	3.1[b]	3.0[b]	5.0[b]	7.9[b]	4.9[b]	5.5[b]	7.9[b]
Zn mg	0.53	5.3[b]	4.1[b]	4.4[b]	3.2[b]	5.5[b]	4.1[b]	4.3[b]	5.5[b]	6.5[b]
Cu µg	175	361[b]	143[b]	297[b]	284[b]	386[b]	336[b]	277[b]	369[b]	413[b]
Mn µg	2.3	27[b]	22	163	22	122[b]	432[b]	338[b]	313[b]	319
Mo µg	0.28	19	21	5.4	16	17	32	32[f]	15	18
Se µg	9.1	5.1[b]	5.0[b]	14	15	25	16[b]	11[b]	13[b]	13[b]
Toxic elements										
As µg	0.39	0.48	0.52	0.65	0.15	0.29	0.85	1.0	0.35	1.4
Cd µg	0.04	0.11	0.07	0.34	0.30	0.25	0.28	0.11	0.12	1.0
Sb µg	0.10	0.08	0.08	0.06	0.03	0.23	0.43	0.22	0.14	0.59
Pb µg	0.35	1.1	0.91	1.0	0.74	0.71	1.2	0.85	1.2	1.3
U µg	0.02	0.07	0.04	0.30	0.15	0.71	0.64	1.2	0.67	1.2

[a] Hypoallergenic formulas for special medical purposes.
[b] Fortified.

fed infant, respectively. Some formulas would also result in higher daily intakes of toxic elements in the formula fed compared to the breast fed infant, particularly Cd and U.

3.2. Infant foods

Table 3 shows the concentrations of all investigated elements in the analysed infant foods, which varied markedly between the different food types. Eight of the food products were based on cereals (five based on rice and one each of spelt, semolina and oat) and one on cow's milk. Five of the foods were fortified with Ca, Fe and Zn by the manufacturer. Two of these were also fortified with Cu and Se, of which one was also fortified with Mn and the other with Mg. One food was fortified with only Ca, while three were not fortified at all. The analysed concentrations agreed with the fortification levels for all but the oat based food, where the analysed concentrations was around 2-fold the concentration provided by the producer. The cereal based foods generally held higher concentrations of Mg, Mn, Mo, As, Cd and Sb than the milk based foods. In particular, the rice-based food had high concentrations of As (17–33 µg/kg) compared to all other foods (0.2–3 µg/kg). Two of the rice-based foods also had high concentrations of the other toxic elements as well as most essential elements. The two foods based on wholegrain rice had markedly lower Se concentrations than the remaining foods, while the oat based food had fairly high concentrations of Mg, Fe, Mo and Pb. Notably, the rice + locust bean based food had by far the highest concentrations of Cd (11 µg/kg) and Cu (1400 µg/kg). The spelt based food (fortified with Ca only) was found at the higher end of Ca, Mg, Mo, Cd and Sb concentrations among the analysed foods.

Table 4 shows the calculated intake of all measured elements in one portion of infant food at 4 months of age and, for comparison, the calculated intake from one feeding of breast milk at the same age. The intake of elements per portion varied greatly between the different foods, but was generally higher than from one feeding of breast milk, especially for Fe (2.5–20 times for non-fortified and 12–141 times for fortified foods), Mn (26–2800 times), Mo (48–460 times), As (1–95 times), Cd (3–270 times), Pb (1–24 times) and U (21–394 times). However, some foods provide less Ca, Cu and Se than breast milk, in particular the two whole-grain rice-based foods where one would provide only 3% Ca, 56% Cu and 24% Se of that in breast milk and the other only 24% Ca and 30% Se.

Fig. 1 illustrates the differences in element intake between the breast fed and the formula fed infants at 1 and at 4 months of age. At 4 months, the difference is presented with and without substitution of two formula meals per day with food. The daily intakes from formula and formula/food are presented as the ratio of the daily intake of the exclusively breast fed infant at corresponding ages, which is set to 1. Daily element intakes from formula alone at 4 months were generally 20% higher than at 1 month of age

Table 3
Concentrations of essential and toxic elements in infant foods intended for consumption from 4 months of age (mean ± SD).

Base		Milk	[a]Semolina	[a]Spelt flour	Oat	[a]Wholegrain rice	[a]Wholegrain rice	[a]Rice + banana	Rice + banana	[b]Rice + locust bean
Essential elements										
Ca	mg/kg	370 ± 63[c]	62 ± 0.91	963 ± 6.9[c]	1413 ± 86[c]	38 ± 0.59	16 ± 0.53	1111 ± 60[c]	1252 ± 51[c]	1659 ± 17[c]
Mg	mg/kg	39 ± 1.7[c]	147 ± 1.1	174 ± 4.1	190 ± 11	127 ± 1.1	110 ± 0.61	127 ± 7.5	117 ± 4.5	233 ± 5.1
Fe	mg/kg	5.7 ± 0.39[c]	3.2 ± 0.04	3.0 ± 0.15	24 ± 1.4[c]	1.2 ± 0.56	1.3 ± 0.08	4.3 ± 0.15[c]	14 ± 0.24[c]	26 ± 0.31[c]
Zn	mg/kg	4.8 ± 0.60[c]	3.2 ± 0.04	5.2 ± 0.04	9.3 ± 0.86[c]	1.5 ± 0.004	1.7 ± 0.01	6.3 ± 0.3[c]	10 ± 0.23[c]	10 ± 0.18[c]
Cu	µg/kg	360 ± 8.2[c]	434 ± 2.6	426 ± 13	333 ± 15	199 ± 1.9	293 ± 2.4	311 ± 8.7[c]	483 ± 15	1400 ± 7.7
Mn	µg/kg	59 ± 8.9	3411 ± 33	2119 ± 51	2366 ± 114	3156 ± 10	2485 ± 19	723 ± 3.8[c]	2158 ± 76	6227 ± 76
Mo	µg/kg	20 ± 1.1	42 ± 0.16	100 ± 0.99	146 ± 7.8	64 ± 1.2	40 ± 0.07	88 ± 3.0	74 ± 2.4	108 ± 1.9
Se	µg/kg	20 ± 0.05[c]	19 ± 0.04	15 ± 0.11	23 ± 0.14	2.4 ± 0.56	6.6 ± 0.32	28 ± 0.84[c]	15 ± 0.66	16 ± 1.1
Toxic elements										
As	µg/kg	0.23 ± 0.05	1.0 ± 0.04	2.4 ± 0.11	3.3 ± 0.14	33 ± 0.56	30 ± 0.32	17 ± 0.84	18 ± 0.66	32 ± 1.1
Cd	µg/kg	0.28 ± 0.14	3.6 ± 0.07	3.8 ± 0.07	2.4 ± 0.19	1.7 ± 0.04	0.39 ± 0.02	1.3 ± 0.05	4.0 ± 0.12	11 ± 0.27
Sb	µg/kg	0.04 ± 0.01	0.14 ± 0.01	0.97 ± 0.01	0.18 ± 0.01	0.14 ± 0.04	0.14 ± 0.01	0.26 ± 0.02	2.8 ± 0.09	1.0 ± 0.04
Pb	µg/kg	1.2 ± 0.19	1.1 ± 0.08	1.8 ± 0.12	3.1 ± 0.23	1.2 ± 0.12	1.3 ± 0.09	3.3 ± 0.15	13 ± 0.23	3.1 ± 0.11
U	µg/kg	0.30 ± 0.16	0.47 ± 0.01	0.53 ± 0.01	0.22 ± 0.003	0.49 ± 0.01	0.02 ± 0.002	0.67 ± 0.03	3.2 ± 0.12	2.6 ± 0.05

[a] Organic.
[b] Hypoallergenic, gluten-, lactose- and cow milk protein free, with locust bean gum from St. John's bread.
[c] Fortified.

Table 4
Element intakes from one portion of each food (67–225 g) at 4 months of age and one portion of breast milk (140 g) at 17 weeks (4.25 months) of age.

Base	Breast milk	Milk	[a]Semolina	[a]Spelt flour	Oat	[a]Rice	[a]Whole-grain rice	[a]Rice + banana	Rice + banana	[b]Rice, locust bean
Portion size (g)	140	200	225	140	175	225	67	100	133	200
Essential elements										
Ca mg	35	74[c]	14	135[c]	247[c]	8.5	1.0	111[c]	167[c]	332[c]
Mg mg	5.2	7.8[c]	33	24	33	29	7.4	13	16	47
Fe μg	36	1145[c]	730	425	4149[c]	266	89	430[c]	1801[c]	5151[c]
Zn μg	106	962[c]	728	724	1627[c]	341	111	632[c]	1363[c]	2021[c]
Cu μg	35	72[c]	98	60	58	45	20	31[c]	64	280
Mn μg	0.45	12	768	297	414	710	166	72[c]	287	1245
Mo μg	0.06	4.0	9.4	14	26	14	2.7	8.8	9.9	22
Se μg	1.8	4.0[c]	4.2	2.1	4.0	0.55	0.44	2.8[c]	2.0	3.1
Toxic elements										
As μg	0.08	0.05	0.22	0.33	0.57	7.3	2.0	1.7	2.3	6.5
Cd μg	0.01	0.06	0.82	0.53	0.43	0.38	0.03	0.13	0.54	2.3
Sb μg	0.02	0.01	0.03	0.14	0.03	0.03	0.01	0.03	0.38	0.20
Pb μg	0.07	0.23	0.25	0.25	0.55	0.26	0.09	0.33	1.7	0.63
U μg	0.004	0.06	0.10	0.07	0.04	0.11	0.001	0.07	0.43	0.52

[a] Organic.
[b] Hypoallergenic, gluten-, lactose- and cow milk protein free, with locust bean gum from St. John's bread.
[c] Fortified.

due to higher milk intake. For Ca, Mg, Cu, Se and Sb, the average daily intakes from formula at one and at 4 months of age were relatively similar to that of the exclusively breast fed infant, also when food was introduced. There was however, a larger variation in daily intakes of Ca, Mg and Cu with the introduction of food depending on food type. Some foods also resulted in decreased intakes of Cu and Se compared to exclusive formula feeding at 4 months. Intake of Fe and Zn remained about the same when food was added, although much higher than the intake of the breast fed infant. Since the concentrations of Fe and Zn varied more between foods than between formulas, introduction of food results in a greater variability in daily intakes, with some foods resulting in Fe intakes over 100 times that of the breast fed infant. The largest increases in intake with the introduction of food were found for Mn, Mo, As and Cd. Once two meals of complementary food are introduced at 4 months of age, daily Mn intake would increase from 14–300 to 20–1500 times that of the exclusively breast fed infant. The intake of Mo would also increase significantly with the introduction of complementary foods, from 30–170 to 40–330 times the intake of the breast fed infant. For As and Cd, daily intakes would increase from 1–5 and 2–40 times, respectively, to 1–50 and 3–150 times with the introduction of food. Both the amount and variation of daily Pb intake would increase with the addition of cereal based products to the infant's diet, while the intake of U would decrease with regard to the median intake from the investigated foods. Intake of U shows a large variation both with and without food.

4. Discussion

4.1. General

The present study demonstrated wide variations in the concentrations of most essential and toxic elements in infant formula and

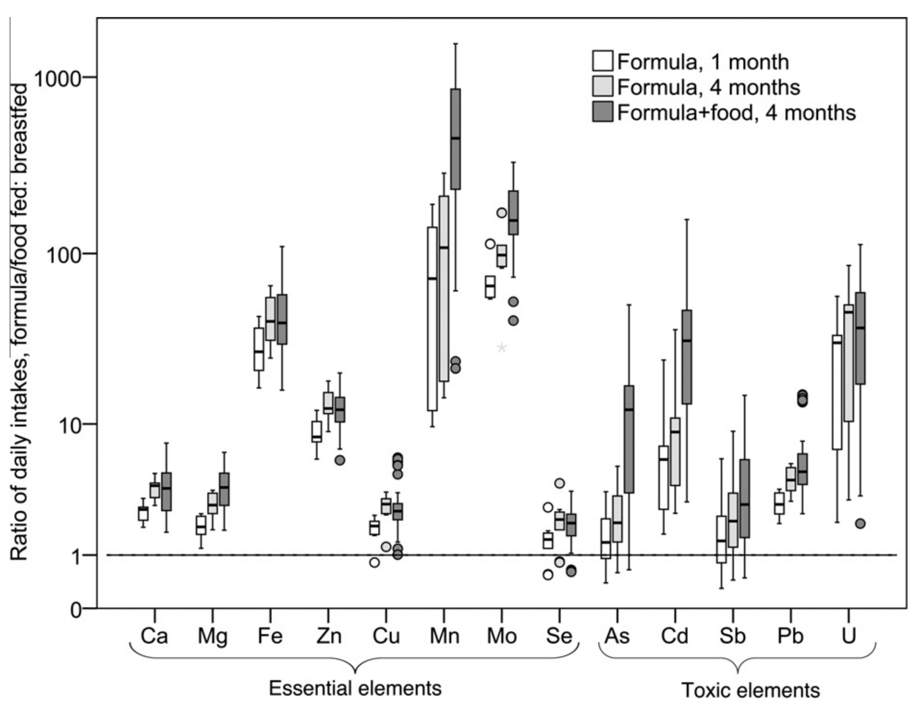

Fig. 1. Ranges of daily element intakes from infant formula at 1 month of age, at 4 months of age and from formula + food at 4 months, respectively. Intakes are presented as a ratio of intakes for the exclusively breast fed infant at corresponding ages set to 1. The *y*-axis is log transformed.

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foods, largely determined by the ingredients used. In infant formula, the manufacturer's fortification of essential elements and using soy protein resulted in levels of essential elements, especially Fe, Zn, Mn and Mo, many times higher than those found in breast milk as shown in Fig. 1. The main concerns with regard to adverse health effects are thus the high concentrations of Mn in formula (up to 0.5 mg/l in the ready-to-eat products prepared with deionised water) and possibly Fe (up to 9 mg/l, all fortified) and Mo (up to 37 μg/l), as well as the low concentrations of Se in some formulas. In addition, both soy based and cow's milk based formulas had surprisingly high Cd concentrations (1.2 and 0.4 μg/l, respectively).

In infant foods, the high concentrations of As in the rice-based foods (~30 μg/kg) are of particular concern. The infant foods also frequently had elevated concentrations of Cd (up to 11 μg/kg), Sb (3 μg/kg), Pb (13 μg/kg) and U (3 μg/kg). Notably, two of the rice-based foods had high concentrations of all toxic elements as well as all essential elements except Se. Of the essential elements, the high concentrations of Mn (6 mg/kg), Fe (26 mg/kg) and Mo (146 μg/kg) in some foods may be of concern, considering the low intake of these elements in the breast fed infant. The large increase in daily intakes of Mn, Mo, As, Cd and U with the introduction of foods at a few months of age is likely a result of these elements naturally being mainly derived from cereals rather than dairy products.

The results presented in this paper were all measured after mixing powdered infant formulas and foods with deionised water. The results therefore represent conservative concentrations as essential and sometimes also toxic elements frequently occur in the more commonly used tap or bottled water. For example, a common water quality problem worldwide is the presence of elevated concentrations of Mn, which can substantially increase the final Mn concentration in the ready-to-eat product (Sievers, 2005). Naturally elevated As levels in drinking water are also common in many countries worldwide, while Pb in water pipes and fittings can contribute to drinking water Pb concentrations (WHO, 2006). Moreover, many infant foods are to be mixed with infant formula which would further increase the total metal content of the ready-to-eat product.

4.2. Iron

In the present study, all formulas and five out of nine foods intended for consumption during the first 6 months of life were fortified with Fe up to 9 mg/l and 26 mg/kg, respectively, i.e., well above common breast milk concentrations of <1 mg/l. High Fe levels in infant formula have been justified by low bioavailability as well as concern for Fe deficiency in infants. However, Fe bioavailability from milk based infant formulas has increased in recent years due to formula modifications and are now similar to breast milk (Hertrampf, Olivares, Pizarro, & Walter, 1998; Koletzko et al., 2005). In addition, the risk for Fe deficiency is low before 6 months of age in healthy term infants due to sufficient Fe stores at birth (Lönnerdal, 2008). While Fe absorption in adults is controlled via tight regulation of the divalent metal transporter 1 (DMT1) (Gunshin et al., 2001), infants lack the ability to regulate its expression. It has been suggested that DMT1 is not fully functional until 6–9 months of age (Domellöf, Lönnerdal, Abrams, & Hernell, 2002; Lönnerdal & Kelleher, 2009) and as a result, Fe may be absorbed at levels above those required. Concurrently, humans do not seem to have a system of excreting Fe, and thus consequences of excessive intake must be considered (Berglund, Westrup, & Domellöf, 2010). Excessive Fe intake is therefore of particular concern in Fe replete infants (Lönnerdal & Kelleher, 2009), and has been associated with impaired growth and increased morbidity (Dewey et al., 2002). There is also concern for effects on cognitive development and impaired immune function (Buonocore et al., 2003; Domellöf et al., 2001; Kon et al., 2010; Sullivan, 2008).

The optimal Fe intake for infants has not yet been established (Berglund et al., 2010), but a fortification level of 2 mg/l in milk based formulas has been proposed sufficient for healthy term infants (Koletzko et al., 2005; SCF, 2003). In a study on Swedish infants, Hernell and Lönnerdal (2002) concluded that a concentration of 1.6 mg Fe/l formula met the requirement of infants aged 6 months or younger. A higher concentration added no extra benefit, as suggested by similar haemoglobin and Fe status of infants fed formula containing 1.6 and 4 mg Fe/l. However, Fe requirements of preterm and low birth weight infants are higher as the main Fe supply to the foetus occurs in the last trimester (SCF, 2006). Subsequently, these infants are at high risk of developing Fe deficiency or Fe deficiency anaemia (Berglund et al., 2010). Berglund et al. (2010) reported that in marginally low birth weight infants (2000–2500 g), a daily intake of 0.6 and 1 mg Fe/kg body weight from 6 weeks to 6 months of age provided protection against Fe deficiency and Fe deficiency anaemia, respectively, corresponding to around 4 and 7 mg/day for the 1 and 4 month old infant, respectively. Table 2 shows that three of the analysed infant formulas do not provide sufficient daily Fe supplies to the low birth weight infant at 1 month of age, while the formula with the highest Fe concentration provides almost twice as much as required. Similarly, based on our assumption of three meals of formula and two meals of food per day, the daily Fe intake at 4–6 months would be 2–16 mg, with most formulas and foods providing sufficient Fe to the low birth weight infant but excess to the term infant. Considering that most infants in Sweden are born at term (Berglund et al., 2010), and that preterm and low birth weight infants are often recommended Fe supplementation (Edmond & Bahl, 2006), the necessity of Fe concentrations in formula that well exceed levels that are considered sufficient to the majority of infants is questionable. Similarly, a Fe concentration of 9 mg/l in the soy based formula may also be at the high end as a fortification level of 3 mg/l was considered sufficient in soy based products for populations at risk of Fe deficiency, also in consideration of lower bioavailability in soy based products (Koletzko et al., 2005).

4.3. Manganese

Similar to Fe, many infant formulas are fortified with Mn, although deficiency is virtually unknown in humans and evidence of its toxicity is growing (Hardy, 2009; Menezes-Filho, Bouchard, Sarcinelli Pde, & Moreira, 2009). The fortified formulas held up to 150 times more Mn than what is usually found in breast milk. The high concentration of Mn in the soy based formula (367 μg/l, not fortified) is likely due to high concentrations in soy (Cockell, Bonacci, & Belonje, 2004). Phytate in soy based products decreases the bioavailability of a number of essential elements, including Ca, Fe, Zn and Mn (Lönnerdal, 1997), but there is no clear consensus on Mn bioavailability in milk based formulas in infants (Koletzko et al., 2005). For example, low Mn bioavailability in infant formula compared to breast milk was demonstrated in adults (Davidsson, Cederblad, Lönnerdal, & Sandström, 1989), while a balance study in 2–16 week old infants showed similar Mn absorption (%) in those fed breast milk (mean 6.2 μg Mn/l) as in those fed two different types of formula (77 and 99 μg Mn/L) (Dörner et al., 1989). Consequently, while the bioavailability was similar, the retained amount of Mn from formula was 6 times greater than from breast milk because of the higher concentration in formula (Dörner et al., 1989). In infant formula and in water, Mn is mainly present in its divalent form (Erikson, Thompson, Aschner, & Aschner, 2007), while Mn appears mainly bound in its trivalent form to lactoferrin in breast milk (Coni, Bocca, Galoppi, Alimonti, & Caroli, 2000). In addition to Fe, DMT1 is also responsible for the absorption of Mn, Cd and Cu (Garrick et al., 2006). As a result of undeveloped expression of DMT1 in infancy as discussed above, Mn in its divalent form may similarly to Fe be absorbed at levels above those required.

Although breast milk contains only a few μg Mn/l, the guidance upper limit (GUL) of Mn in infant formula is set at 670 μg/l (Codex Alimentarius Commission, 2007). All formulas were below this limit. However, this value is not based on scientific data and does not consider the increasing evidence of neurotoxicity in children (Ljung & Vahter, 2007). On the contrary, it is justified by being below the lowest observed adverse effect level (LOAEL) of Mn exposure from drinking water in adults (SCF, 2003), which in turn is based on misinterpretations and is also irrelevant for infant nutrition (Ljung & Vahter, 2007). Recently, Menezes-Filho et al. (2009) reviewed studies on health effects in children environmentally exposed to Mn and found that most studies reported neuropsychological effects, such as poorer cognitive outcome and hyperactivity with elevated postnatal exposure. Exposure sources ranged from industrial pollution and mine wastes to drinking water and food, including infant formula. A number of experimental animal studies of Mn exposure early in life support the observed neurotoxic effects (Golub et al., 2005; Tran, Chowanadisai, Crinella, Chicz-Demet, & Lönnerdal, 2002; Tran, Chowanadisai, Lönnerdal et al., 2002).

The minimum level for Mn in infant formula is based on the mean concentration in breast milk (3–4 μg/l) and set slightly higher at 7 μg/l with regard to the lower absorption from cow's and soy milk (SCF, 2003). This generous range of Mn concentrations (7–670 μg/l) allowed in infant formula reflects the lack of scientific data on infant requirements and its potential toxicity (Agostoni & Domellöf, 2005). Similarly, no upper limit for Mn intake has been set for infants younger than 6 months because of considerable uncertainties (SCF, 2003). However, there are recent indications that low chronic exposure has adverse effects as suggested by a study on Canadian children, which found a significant association between relatively low Mn concentrations in drinking water (median of highest quintile 216 μg/l) and lower IQ scores (Bouchard et al., 2010). WHO has set a health based guideline value for manganese in drinking water at 400 μg/l, because of the risk for neurotoxic effects at high exposure (WHO, 2004). Since Mn is a common ground water problem, with natural ground water concentrations ranging from a few μg/l to several mg/l, the potential for significant additions from drinking water thus need to be considered in the ready-to-eat product. The increasing evidence of Mn toxicity and its presence in water indicate that concentrations of several hundred μg/l, which we found in about half of the investigated formulas, may in fact not be safe for the infant.

4.4. Molybdenum

There is a lack of studies on the adequate Mo intake in early life, although it seems likely that the fairly low concentrations in breast-milk (<1 μg/l) are sufficient. In the present study, the Mo concentrations of infant formula and food were up to 100-fold and several 100-folds higher, respectively, than the average found in breast milk. The reason for this difference is likely due to naturally high Mo concentrations in cow's milk (around 50 μg/l) and in cereals (SCF, 2003). A study on Mo bioavailability in ten 20-day old preterm infants fed extrinsic labelled ^{100}Mo with a feed of formula or breast milk found that on average 36% (range 13–56%) of ingested Mo was retained (Sievers, Dörner, Garbe-Schonberg, & Schaub, 2001). Thus, the formulas investigated in the present study would provide a daily retention of 2–35 μg, i.e., many times more Mo than from breast milk. High Mo intake has been shown to result in increased urinary Cu excretion, but the effect of this interaction is currently unknown (Sievers et al., 2001; Sievers, Schleyerbach, & Schaub, 2004).

4.5. Selenium

In contrast to all the other investigated elements, two formulas were found to provide less Se than breast milk and also less than the recommended daily intake of 6 μg/l (WHO/FAO, 2004). This is surprising, considering that Se is taken up more easily from breast milk than from formula, as indicated in studies showing that breast fed infants consistently show better Se status than formula fed infants (reviewed in Dorea, 2002). However, more information is required as to the forms of Se in different formulas and foods. Selenium is an essential component of numerous low-molecular-weight compounds and selenoproteins, the functions of which include redox regulation of intracellular signalling, redox homeostasis, and thyroid hormone metabolism (Papp, Holmgren, & Khanna 2010). Although infants are born with Se reserves, they also depend on external sources, such as milk (Dorea, 2002). This is particularly important in the case of exposure to pro-oxidants.

4.6. Arsenic

Several recent studies have shown that rice, including rice-based baby food, often contains elevated concentrations of As, most of which is in the most toxic inorganic form (Meharg et al., 2008, 2009; Signes-Pastor et al., 2008). Inorganic As is highly reactive and causes a wide range of toxic effects besides cancer, and for many of those, children may be particularly susceptible (Vahter, 2008, 2009). In fact, early-life exposure to fairly low levels of inorganic As in drinking water has been associated with increased infant morbidity and mortality, as well as impaired child development (Rahman et al., 2007, 2009; Wasserman, Liu, Factor-Litvak, Gardner, & Graziano, 2008). The potential for high As concentrations in any rice-based products intended for infants requires special attention. No rice-based formulas were found for analysis in the present study but hydrolysed rice protein formulas have recently been presented as good alternatives to infants with cow's milk protein allergy (Fiocchi et al., 2006; Reche et al., 2010), the most common infant food allergy in developed countries with a prevalence of 2–3% (Høst, 2002). In the present study, the three purely rice-based foods had As concentrations around 30 μg/kg, while two foods with added fruit had slightly lower concentrations (~18 μg/kg). Just one portion of rice-based food could contribute as much as 7 μg As, i.e., about 1 μg/kg body weight. Two portions per day would thus come very close to the former tolerable daily intake (TDI) of 2.1 μg/kg bodyweight, which is no longer considered appropriate to protect health (EFSA, 2010). For comparison, the drinking water standard for inorganic As of 10 μg/l in most countries contributes less than 0.3 μg/kg body weight per day in an adult person. Even this level of exposure is associated with an appreciable cancer risk (NRC, 2001). However, Fängstrom et al. (2008) reported low As concentrations of about 1 μg/l in breast milk of Bangladeshi women consuming drinking water with a wide range of inorganic As (up to 1000 μg/l), indicating that very little As is excreted in breast milk. The finding of elevated intakes of As from rice-based food products raises the question of the suitability of rice in infant foods. In the UK, children younger than 4.5 years are advised against consuming rice milk because of concern for high As exposure (Food Standards Agency, 2009). In Denmark, children below 10 kg (~3 years) are advised against consuming rice milk for the same reason (Fødevarestyrelsen, 2009).

4.7. Cadmium

Long-term excessive Cd intake may cause adverse effects on kidney function and bone mineralisation. The European Food Safety Authority (EFSA) recently lowered the Tolerable Weekly Intake from 7 to 2.5 μg/kg bodyweight in the light of new evidence of adverse effects, and noted that the average adult weekly dietary

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exposure in Europe is around this level (EFSA, 2009). However, little is known about early-life exposure and associated adverse effects, although absorption of Cd appears to be higher in infants than in adults (Kippler, Hoque et al., 2010). Calculated weekly intakes of Cd from the investigated formulas vary between 0.10 and 1.5 μg/kg body weight at six weeks of age, compared to 0.06 μg/kg bodyweight from breast milk. Introduction of rice-based foods may increase the weekly intake to 5 μg/kg body weight (3 meals of formula + 2 meals of food) for the four month old infant. Recent studies from rural Bangladesh showed elevated urinary Cd concentrations in three month old infants, indicating high rates of intestinal absorption, probably because of the immature regulation of the transport system for divalent metal ions, as discussed above (Kippler, Nermell, et al., 2010). Possibly, the developing kidney is particularly susceptible to Cd, as both glomerular and tubular functions continue to develop until 2–3 years of age (Sekine & Endou, 2009). In addition, recent studies indicate that Cd has oestrogen-like effects in the case of early-life exposure (Johnson et al., 2003).

4.8. Lead

Lead is a well-documented neurotoxic metal. The studied infant formulas varied little in Pb content; all had 0.5–1.7 μg/kg. The food products varied more with one containing 12.5 μg/kg, which would provide more than 20 times as much Pb as breast milk. The European CONTAM Panel, following a review of available Pb data, considered that the PTWI for Pb in food is no longer appropriate as there is no threshold level for lead under which there is no risk of adverse health effects in young children. A new guidance level could thus not be established (EFSA, 2010).

5. Conclusion

Infant formulas and foods must supply the growing infant with adequate amounts of essential elements, but must not jeopardise their health by excessive exposure. It has been shown that infant formulas contribute significantly higher amounts of many essential elements, especially Fe, Mn and Mo, than breast milk. With regard to the growing evidence of effects on cognitive development from both excessive Fe and Mn intake, more research on the bioavailability and role of speciation is urgently needed. Moreover, the large variation of especially Mn and Fe found in the investigated formulas raises the question of what we really know about the infant's requirement of these elements, and the need for their fortification to such high concentrations. It should be noted that infants have both higher absorption and less effective excretion of several elements compared to adults (Oskarsson, Palminger Hallen, Sundberg, & Petersson Grawe, 1998). Also, intake of concentrations which are not utilised or stored in the body needs to be excreted, which contribute an unnecessary burden on metabolic and other physiologic functions of the infant (Koletzko et al., 2005). The daily intake of all essential elements, and especially Mn, Fe and Mo, increase with the introduction of complementary foods. Alarmingly, these complementary foods may also introduce high amounts of toxic elements such as As, Cd, Pb and U, mainly from their raw materials. These elements have to be kept at an absolute minimum in food products intended for infant consumption.

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