Safety assessment of essential and toxic metals in infant formulas

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The aim of this study was to assess toxic metal (Cd, Pb and Al) contamination and levels of three essential trace elements (Mn, Cr and Co) in 63 infant formulas. In addition, the levels of these metals in the study samples were compared with the acceptable limits of toxic heavy metals and the recommended daily allowances (RDAs) of essential trace elements. According to our results, the toxic metal levels measured in the formulas were within the acceptable limits, with the exception of Al levels in 8 of the 63 samples. In 16 samples, Mn levels exceeded 600 μg/day, and the Cr content in 7 samples was higher than 5.5 μg/day, these amounts being the adequate intake levels for infants. Cobalt levels in 10 formulas were higher than the RDA. In view of these findings, which indicate that metal levels in infant formulas are generally much higher than those found in breast milk, breast milk should be preferred for infant feeding. Moreover, since infants are potentially more susceptible to metals, infant foods should be monitored regularly and checked for contamination by toxic metals as well as for levels of essential trace elements.

***Key words:** infant food, toxic metals, essential elements, provisional tolerable weekly intake (PTWI), recommended daily allowance (RDA), adequate intake*

Breast-feeding is the optimal mode of nutrition for infants. However, commercially available infant formulas provide a suitable alternative, especially when breast-feeding is not possible and/or not adequate[1]. The presence of contaminants such as metals in infant formulas may pose health risks for children[2]. Therefore, cumulative exposure from such formulas should not exceed the provisional tolerable weekly intake (PTWI) for toxic metals as set by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the recommended daily allowance (RDA) for essential trace elements. When the RDA cannot be determined, adequate intake can be used as a recommended intake value[3,4]. Cadmium (Cd), lead (Pb) and aluminium (Al) occur naturally in the environment, and the general population is exposed to these toxic metals from multiple sources, but the main exposure is via food. After ingestion, approximately 5–10% of Cd and Pb and less than 1% of Al are absorbed. However, the absorption of metals is higher in children than in adults; Pb, in particular, is absorbed up to 42%[5]. Cadmium is primarily toxic to the kidneys, but can also cause bone demineralization. Chronic exposure to Pb can affect numerous body systems, including the central nervous system, the kidneys and the immune system. The target for Al toxicity is primarily the nervous system, and then the skeletal system[1,5].

Trace elements have various roles in biochemical functions. Manganese (Mn), chromium (Cr) and cobalt (Co) are essential for human life at low concentrations; however, they can be toxic at high concentrations. Manganese is required for normal metabolism of amino acids, proteins, lipids and carbohydrates. Manganese also acts as a cofactor for a variety of enzymatic reactions and is necessary for the function of many organ systems. On the other hand, exposure to high levels of Mn causes a type of neurotoxicity commonly referred to as manganism[5]. The essential form of Co is cobalamin, which is a critical component of vitamin B_{12}. However, chronic oral administration of high levels of Co for the treatment of anemia can cause goiter. Epidemiologic studies suggest that the incidence of goiter is higher in regions containing high levels of Co in the water and soil[5]. Chromium is important for maintaining normal glucose metabolism, but excessive consumption can cause chronic renal failure[6].

In this study, various brands of infant formulas used for infant feeding in Turkey were analyzed for possible toxic metal (Al, Cd and Pb) contamination as well as trace element (Co, Cr and Mn) levels. In addition, a safety assessment of these metals in the analyzed infant formulas was conducted, using the PTWI value of toxic heavy metals and the RDA of essential trace elements.

Material and Methods

Sample Collection

Sixty-three different infant foods and formulas from 21 different manufacturers were randomly collected from pharmacies and supermarkets in Ankara, Turkey, in 2006. The items were in their original packages. These samples were divided into 3 groups: cereal-based (a single type or any combination of wheat, rice, corn and oats, n=23), milk-based (a single form or any combination of milk, milk powder, milk fat and milk protein, n=28) and mixed (any combination of cereals, milk, fruit and vegetables, n=12).

Determination of metal content

0.5 g of each sample was digested in a 6:1 mixture of nitric acid (65%, Merck) and hydrogen peroxide (30%, Merck) in a high-performance microwave digestion unit (Milestone MLS-1200 MEGA) prior to determination of metal content.

Analyses were performed using a Varian 30/40 atomic absorption spectrophotometer equipped with a Varian GTA96 graphite tube atomizer and a Varian DS-15 data station (Mulgrave, Victoria, Australia). A Varian autosampler was used to inject 10 μl sample aliquots into apyrolytically coated graphite tubes (5.8 mm i.d., 80 mm o.d. and 28.0 mm long). Instrumental parameters are presented in Table I. Measurements were performed using hollow cathode lamps operated at 10 mA at a slit width of 0.5 nm. Argon was used as the inert gas, with a flow rate of 3.0 ml/min during all stages except atomization.

Calculation of daily intake of the analyzed metals

Daily exposures of the metals were estimated using the mean metal levels in the analyzed formulas (Table II) according to the feeding tables and dosages recommended by the manufacturers (Table III), and daily intakes of the analyzed metals in infant formulas were presented as μg/kg bw/day. Mean daily dietary intake was calculated for 0- to 12-month-old infants of 3.5 to 10 kg in weight (Table III). Based on this table, children up to 12 months of age consume approximately 135 g of infant formula in 1000 ml of infant food per day, while 0- to 2-week-old babies consume 75 g of formula in 500 ml of infant food per day if not fed from other sources. Therefore, for children up to 12 months of age, daily metal exposure is calculated by multiplying the metal levels detected in a gram of formula by 135. For 0- to 2-week-old babies, daily exposure is calculated by multiplying the metal levels detected in a gram of formula by 75.

PTWI values, used by JECFA for contaminants that may accumulate in the body, were divided by 7 to calculate the provisional tolerable daily intake (PTDI)[3]. For example, using the PTWI value for Pb, defined as 25 μg/kg bw/week, we calculated PTDI as 3.6 μg/kg bw/day (Table III).

Statistical analysis

All results were expressed as mean value $\pm$ standard deviation (SD). The differences between the groups were evaluated with the Kruskal-Wallis analysis of variance, and comparisons between two independent groups were made with the Mann-Whitney *U*-test. $p<0.05$ was considered as statistically significant.

Results

The levels of the toxic and essential metals being investigated in infant formulas are presented in Table II. Pb contamination in the milk-based formulas was slightly higher than in other kinds of formulas, but the difference was not significant. The mean Pb level in all samples was 7.14 $\pm$ 4.00 ng/g. Considering the daily intake of formula per day for 2- to

Table I. Graphite Tube Atomizer Parameters for Atomic Absorption Spectrometric Analysis

Parameters	Al	Co	Pb	Cr	Cd	Mn
Wavelength (nm)	309.3	242.5	283.3	357.9	228.8	279.5
Pyrolysis temperature (°C)	1200	2400	1900	2300	500	1300
Atomization temperature (°C)	2300	2450	2450	2450	1500	1900
Measurement time (sec)	3	3	3	3	3	3
Replicates	2	2	2	2	2	2
Standard concentrations (ng/ml)	10-50	10-50	10-50	5-20	0.5-1.5	1.25-5

4-week-old infants weighing 4.2 kg to be 100 g, the mean daily intake of Pb was calculated as 0.71 μg, which is 4.72% of PTDI (Tables III and IV). The highest Pb level (24.90 ng/g) in infant formulas was also used to calculate the maximum exposure value, and the results did not exceed the PTDI values recommended by JECFA (Table IV).

Cadmium levels in milk-based samples were significantly lower than in the mixed and cereal-based infant foods ($p<0.001$) (Table II). There were no statistically significant differences between the mixed and cereal-based samples ($p=0.578$). Mean daily Cd intake was calculated for 0- to 12-month old babies as shown in Table III, and the results were found to be under the PTDI value (range, 7.68–13.54 % of PTDI) (Table IV). According to our exposure assessment using the highest Cd level (27.23 ng/g) in cereal-based infant formula, the daily Cd intake was 0.64 μg/kg bw/day for 2- to 4-week-old babies weighing 4.2 kg.

Aluminium levels in the milk-based, cereal-based and mixed infant formulas were not different (Table II). The mean level in all samples was 8.02 ± 8.67 μg/g (within the range of 1.70-42.35 μg/g). The mean daily Al intake levels in the formulas investigated (Table III) for 0- to 12-month old babies were under the PTDI value (37.88-66.80 % of PTDI), as shown in Table IV. The highest daily Al intake from infant formula with highest Al content (42.35 μg/g) was calculated as 1008.3 μg/kg bw/day for 2- to 4-week-old babies weighing 4.2 kg.

Manganese content in the samples was 5.72 ±

Table II. Metal Levels in Three Different Groups of Infant Formulas

Groups	Toxic elements			Essential elements		
	Pb (ng/g)	Cd (ng/g)	Al (ng/g)	Mn (μg/g)	Cr (ng/g)	Co (ng/g)
Milk-based (n= 28)						
Mean ± SD	7.68±4.08	0.96±1.46	8.02±8.61	5.73±13.52	40.76±59.10	120.93±80.07
Min-Max	3.75-24.90	ND-7.49	2.40-35.55	0.49-60.36	10.15-240.03	53.65-380.17
Median	6.58	0.52	5.36	0.93	18.38	95.45
Cereal-based (n= 23)						
Mean ± SD	6.96±4.31	8.88±8.79*	7.94±10.33	7.18±5.87*	42.57±44.95	28.29±29.62*
Min-Max	0.55-17.45	0.04-27.23	1.70-42.35	ND-21.69	12.55-218.48	0.55-104.95
Median	6.30	5.54	4.54	6.04	29.45	17.70
Mix (n= 12)						
Mean ± SD	6.22±3.26	5.50±4.29*	8.19±5.35	2.91±2.40#	39.44±19.67	58.82±30.15*#
Min-Max	1.80-12.20	0.46-13.16	2.16-19.46	0.02-6.49	10.90-80.65	23.65-127.15
Median	6.18	3.62	6.65	3.44	42.08	50.00
Total (n=63)						
Mean ± SD	7.14±4.00	4.72±6.67	8.02±8.67	5.72±9.75	41.17±48.04	75.28±71.26
Min-Max	0.55-24.90	ND-27.23	1.70-42.35	ND-60.36	10.15-240.03	0.55-380.17
Median	6.25	1.63	4.97	3.18	27.45	64.25

n: number of samples; ND: non-detectable; *$p<0.05$ vs. milk-based infant foods; #$p<0.05$ vs. cereal-based infant foods.

9.75 μg/g. There were statistically significant differences between the Mn levels of mixed and cereal-based infant foods (p=0.014) as well as between milk-based and cereal-based infant foods (p=0.016). Manganese levels in the mixed group were close to those of milk-based samples (p=0.637). When we compare the results with the adequate intake value of Mn for infants (Table III), 16 samples were seen to exceed 600 μg/day.

The mean chromium level in the infant formulas was 41.17 ± 48.04 ng/g (within the range of 10.15-240.03 ng/g). There were no significant differences between the groups for Cr level (Table II). Seven of 63 samples exceeded the adequate intake value (5.5 μg/day) for infants (Table III).

The mean cobalt level in the formulas was 75.28 ± 71.26 ng/g; the levels in milk-based samples were significantly different than those in cereal-based ones (p<0.001). Mixed samples were found to have a significantly higher Co content than cereal-based (p=0.001) and a lower content than milk-based samples (p=0.001).

Discussion

The present study demonstrates the level of essential elements (Co, Cr, and Mn) and the presence of toxic elements (Al, Cd, and Pb) in 63 infant formulas. Lead contamination in the milk-based formulas was slightly higher than in other kinds of formulas, but not significantly different. Although Pb levels were high in some infant food products, the results were still lower than the PTWI values recommended by JECFA[7] and consistent with a previous study conducted in the Polish market[8]. However, children are more susceptible to the effects of Pb exposure than are adults, and there is no safe blood Pb level for children[9]. In previous studies, Pb content in baby formula was found to be below the limit of detection (0.2 μg/g) in Slovakia[10] and (0.55 μg/ L) in Turkey[11]. Moreover, in a Canadian survey, the mean Pb concentrations in milk-based formulas were 9 times lower (ranging between 0.14 and 2.46 ng/g) than in our study[12]. Considering that there is no safe Pb level for children, Pb contamination in infant foods should be monitored regularly[13,14].

The Cd content of formulas in our study (4.72 ± 6.67 ng/g)[15] was similar to the levels reported by other researchers [8,10]. Cd levels in milk-based samples were significantly lower than in the mixed and cereal-based infant foods. This appeared to be due to the introduction of many more materials into the formula from the various sources of the formula or the manufacturing processes. However, Cd levels in milk-based Canadian formulas were approximately 24 times lower (0.23 ng/g) than our levels[12]. Although the estimated Cd exposure was under the PTDI (0.83 μg/kg bw/day), it was very close to the limit value (78.31 % of PTDI)[16]. Considering that infant foods presumably provide more Cd than breast milk, and long-term excessive Cd intake may cause adverse effects on kidney function and bone mineralization, Cd levels should be kept to a minimum in infant foods[17].

The mean Al level in all samples was 8.02 ± 8.67 μg/g (within the range of 1.70-42.35 μg/g). The highest daily Al intake from infant formula with highest Al content was calculated

Table III. Calculation of Daily Intakes of Analyzed Metals in Infant Formulas

Age	Daily consumed powder formula 'g'	Mean body weight (bw) of baby 'kg'	μg/kg bw/day					
			Pb	Cd	Al	Mn	Cr	Co
0-2 weeks	75	3.5	0.15	0.10	171.9	122.59	0.88	1.61
2-4 weeks	100	4.2	0.17	0.11	191.0	136.21	0.98	1.79
2 months	110	4.7	0.17	0.11	187.8	133.89	0.96	1.76
4 months	145	6.5	0.16	0.11	179.0	127.62	0.92	1.68
6 months	135	7.5	0.13	0.08	144.4	102.97	0.74	1.36
6-12 months	135	10	0.10	0.06	108.3	77.23	0.56	1.02

"Daily consumed powder formula" and "mean body weight of baby" values were obtained from feeding tables and dosages recommended by manufacturers.

Table IV. Percentage of Provisional Tolerable Daily Intake (PTDI) of Analyzed Toxic Metals and Percentage of Adequate Intake or RDA of Analyzed Essential Metals

Toxic metals	Pb	Cd	Al	Essential metals	Mn	Cr	Co
PTWI μg/kg bw/week	25	5.8	2000	RDA μg/day	-	-	12
PTDI μg/kg bw/day	3.6	0.83	286	Adequate Intake μg/day	3-600	0.2-5.5	-
Age		% of PTDI		Age		% of Adequate Intake/RDA	
0-2 weeks	4.25	12.19	60.12	0-2 weeks	20.43	16.04	13.44
2-4 weeks	4.72	13.54	66.80	2-4 weeks	22.70	17.82	14.94
2 months	4.64	13.31	65.66	2 months	22.32	17.52	14.68
4 months	4.42	12.69	62.59	4 months	21.27	16.70	13.99
6 months	3.57	10.24	50.50	6 months	17.16	13.47	11.29
6-12 months	2.68	7.68	37.88	6-12 months	12.87	10.11	8.47

PTWI: Provisional tolerable weekly intake; PTDI: Provisional tolerable daily intake; RDA: Recommended daily allowance; Adequate Intake for 0- to 12-month old infant.
% of PTDI/Adequate Intake/RDA: These values are calculated using the μg/kg bw/day metal levels in Table III.

as 1008.3 μg/kg bw/day. However, intake of Al should not exceed the PTDI of 286 μg/kg bw/day, according to the new JECFA standard, and Al levels in 8 infant formulas tested were above the PTDI[18]. In addition, the current Al level in infant formulas was higher than our previous results (range, 1.21-10.93 μg/g)[19]. In another study carried out in Turkey, the Al level was found to be under the upper limits, with a mean range of 10.7-66.8 ng/g[20]. Our results were considerably higher than the Canadian survey, which found a range of 10-3400 ng/g[12], and also a Spanish study, where the highest intake was found to be 15% PTDI[21]. Considering that the Al level is higher in infant formulas than in breast milk, and infants are more susceptible to exposure to Al than adults, precautions should be taken against Al contamination in infant formula, especially with regard to packaging materials containing Al, since this is a potential source of contamination[1].

Assessing Mn levels in our samples, with an average of 5.72 ± 9.75 μg/g[22], we noted that 16 samples exceeded the adequate intakes for Mn[4]. Infants are more sensitive than adults due to a higher absorption and lower basal excretion rate of Mn[23]. Mn levels in cereal-based and mixed infant foods were significantly higher than in milk-based formulas, indicating a need for follow-up studies to examine the Mn intake of children[24]. In another Turkish study[20], the levels of Mn, Cr and Co in infant food were in the range of 0.22-7.20 μg/g, 2.02-68.8 ng/g and 2.62-25.4 ng/g, respectively. These results were considerably lower than those found in our study. At the same time, studies have suggested that the mean daily Mn intake of formula-fed infants is greater than that of breast-fed infants because of higher levels of this element in infant formulas[25].

The mean Cr level in our infant formulas was 41.17 ± 48.04 ng/g. Our results, within the range of 10.15-240.03 ng/g, were higher than what was found in a Slovenian study (<0.05 μg/g)[10]. Although the Cr concentration in our study paralleled the findings in the Spanish study, these levels were higher than those found in human milk[26]. Furthermore, the Food and Nutrition Board recommends 0.2-5.5 μg/day for infants, and 7 samples exceeded this value[4]. It should be noted that drinking water could also have been a source of Cr contamination[27].

Cobalt levels in our milk-based samples were significantly different than those in the cereal-based samples. This may be due to the various sources of the formulas and the manufacturing processes. The mean Co levels in the formulas were below the recommended level determined by the Expert Group on Vitamins and Minerals (range 8.47-14.94% of PTDI). However, for 10 of the formulas studied, the calculated Co intake was higher than the estimated average intake[28].

To summarize, the toxic metal levels measured in the 63 formula samples were under the PTDI, with the exception of Al levels in 8 samples. The Al levels in these samples were about 3-fold higher than the PTDI, which makes them clearly unsafe. Considering the fact that the PTDI of Al is set for adults, and children are more vulnerable, precautions should be taken to reduce the level of toxic metals in infant formulas, with permanent vigilance required to ensure the healthy nutrition of infants. Previous studies have suggested that high Al levels are the result of manufacturing processes and packaging materials. In order to protect infant health, it is essential to keep contaminants at toxicologically acceptable levels. Trace elements are required for the human body, but when our results were compared with the acceptable values for infants, 16 samples exceeded the adequate intake value for Mn. In addition, the Cr level in 7 and the Co level in 10 of the formulas studied were higher than the adequate intake value and the RDA, respectively. Consequently, infants are likely to be exposed to higher metal levels through infant formula than through breast milk[29]. Moreover, considering that infants who are not breast-fed are especially dependent on formula diets, and that infants are potentially more susceptible, toxic metal contamination and essential metal limits should be regularly monitored during manufacturing.

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