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Estimated daily intake and health risk assessment of toxic elements in infant formulas

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Abstract

In this study, the heavy metal (Al, Mn, Co, Cu, Zn, As, se, Cd, Sn, Pb and Hg) concentrations were determined in a total of seventy-two infant formula samples manufactured by sixteen different brands in Türkiye. During the analyses, inductively coupled plasma MS was used in evaluating the nutritional profile and the toxicological risk associated with the consumption of these products. Given the analysis results, the highest Pb content was found in milk-based 'beginner' formulas (0–6 months, three samples) packed in metal containers. The highest concentration of Mn was found in powdered infant formula (Brand 3) that is suitable for 9–12-month-olds. Mn level was found to be above the limit values in nine samples (12·5 %). Cd level exceeded the limit values in two infant formula samples of Brand 3 (0·038 μg/g) and Brand 15 (0·023 μg/g). Therefore, the mean Cd concentration found here reaches the maximum limit set by the European Union commission legislation. Cu was detected in all infant formulas. The highest concentration was determined in Brand 1 (9–12 months, seven samples) and found to be 2·637 (SD 1·928) μg/g. This value is much higher than the reference values set in the national and international standards. Based on the results achieved here, the estimated daily intake (EDI) and target hazard quotient values for all the metals in infant formulas were found lower than < 1. These findings suggest that the baby foods examined would not pose any health risk. The daily intakes exceeding the baby nutrition values recommended by the WHO would pose health risk since they would exceed the EDI levels.

Key words: Infant formula: Heavy metal: Estimated daily intake: Health risk assessment: Public health

Food safety is an issue that is very important for public health, as specified by the potent regulations, the WHO suggestions and many research studies in the literature[1]. Moreover, due to the complication of the subject, food safety is analysed for toxicological and health[2] threat assessments in terms of both microbiological and chemical risks. Particular attention is paid to newborn nutrition[3,4].

The optimal nourishment for newborns is breast milk. Furthermore, for the past two decades, approximately 67 % of infants have not been completely breastfed for the recommended 0–6 months[1]. Infant formulas are additional supplementary or complementary food products and play an important role in nourishing babies[5], as well as being a major diet source for many newborns and an unmatched resource of food for the first 6 months. These major resources are reconstituted powders that babies consume as substitutions for or supplemental to breast milk. Infant formulas are usually produced using animal or plant sources and generally are dairy/soya-based food products[6].

It is feasible to have numerous infant formulas added with macro and micronutrients, which are necessary for 0–6, 6–9, 9–12 and > 12-month-old infants[5]. Moreover, it is also known that infant formulas contain chemical contaminants, particularly heavy metals, on various levels. All the baby formulas are products that can be used only as substitutes. For this reason, the microbiological and chemical decontamination of infant formulas is necessary to maintain infants' health and, to provide the highest level of qualification, it is necessary to assess them using certain standards[7].

Since infant formulas are important food sources for infants, the contaminants such as heavy metals might pose health risks to young children. Infants are particularly susceptible to toxicity because of lower body weight, rapid growth, immature kidneys, immature liver and reduced capacity for detoxification during the first year of life[8,9].

Cow and goat milks, which are important components of most infant formulas[10], can contain toxic heavy metals due to the foods and water consumed by animals and/or exposure to environmental pollution. Additional sources of impurities

Abbreviations: EFSA, European Food Safety Authority; ICP, inductively coupled plasma; JECFA, Joint FAO/WHO Expert Committee on Food Additives; PTDI, provisional tolerable daily intake; PTWI, provisional tolerable weekly intake.

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include water, utensils, containers and equipment used in the manufacturing, packaging and storage of infant formula[11].

Co, Cr, Mo and se were determined to have significant roles in providing essential elements for babies. There also are non-essential elements, which were determined to be toxic to humans, including Al, As, Cd, Pb, Hg and Sn[1,12]. Many standardised procedures were established for the specification of trace elemental nutrients and trace elements, but there is still an analytical gap to comply with the current and future specifications for conformity to regulations and safety of infant formulas, adult and paediatric nourishments and milk-based products that become more and more complicated in the composition of these products[13].

Pb is categorised into Group 2A: Probably carcinogenic to humans by the International Agency for Research on Cancer[14]. Pb causes several illnesses and even death by affecting various organs (kidney, lung and liver) and systems (nervous, cardiovascular and reproductive systems)[15]. International Agency for Research on Cancer categorised Cd and compounds in Group 1 (carcinogenic to humans)[16]. Increased Cd revelation reasons kidney toxicity, cancer (particularly lung and prostate cancers) and cardiovascular and neurological diseases[17].

International Agency for Research on Cancer categorised As and inorganic As compounds into Group 1[16]. Organic forms and macromolecules of As are known to be less toxic than iAs types; nevertheless, exposure to above-limit doses might pose an important risk to public health and it might cause nerve harm and stomach pains[18]. International Agency for Research on Cancer categorised Hg and iHg into Group 3 but methyl-Hg into Group 2B[19]. After entering the body, Hg can easily reach entire tissues including the brain tissues and cause critical damages in numerous organs, particularly in cardiovascular and respiratory systems[20,21].

Factors causing Al exposure for humans include drinking water, as well as food additives. Nevertheless, Al and compounds seem to be poorly absorbed and then removed with the urine. In a previous study, it was reported that neonates were more sensitive to exposure due to their higher level of intestinal absorption because of the immature gastrointestinal tract[22]. Al toxicity was proven to cause neonates to have disrupted renal function and premature birth, or low birth weight. High Al concentrations in infant formulas were associated with Al intoxication in two infants having neonatal uremia[23].

Mn is an essential compound, but it is also a toxic element. The necessity of Mn is emphasised in national and international regulations setting the boundaries for infant formulas and foods[11]. In many studies, it was reported that children exposed to higher concentrations of Mn had impaired cognitive development and lower IQ or intelligence scores in comparison with their peers[24]. In addition, exposure to high Mn concentrations is thought to increase the risk of attention deficits, hyperactivity or attention deficit hyperactivity disorder and other behaviour and attention problems[25,26].

Cu and Zn are fundamental nutrients for infant health. Extreme Zn intake might decrease the intestinal absorption of Cu[27]. Furthermore, Zn in formulas is at a lower level in comparison with breast milk[28]. Zn plays a significant role in the regulation of cell division and cellular division. Indications of Zn insufficiency include disrupted growth and altered cognition in children, as well as diarrhoea, loss of appetite, sensitivity to infections and skin lesions. Excessive Zn intake is usually thought to be relatively non-toxic. Cu is required for cellular metabolism in enzymatic and non-enzymatic systems. Cu insufficiency is uncommon; however, it was observed in pre-term infants and infants recovering from malnutrition accompanied by diarrhoea[27]. A decrease in Cu intake causes disrupted growth, anaemia and increased infection risk. Some toxic effects were related to the increased chronic exposure to Cu, including acute gastrointestinal symptoms such as abdominal pain, vomiting and diarrhoea[29].

The determination of the heavy metal concentrations in infant formula and the contaminant intake is necessary for risk assessment and research on potential contamination that would pose a health hazard for infants. For most of the well-documented ingredients, reference values and safety limits are determined by the authorities such as the European Food Safety Authority (EFSA), the Scientific Committee on Food, Joint FAO/WHO Expert Committee on Food Additives (JECFA) and WHO. The safety limits were given as tolerable daily/weekly intake, provisional tolerable weekly intake (PTWI) and provisional tolerable daily intake (PTDI).

The present study aims to determine the concentrations of eleven metal (Al, Mn, Co, Cu, Zn, As, se, Cd, Sn, Pb and Hg) levels in sixteen different brands' powdered infant formulas (seventy-two samples) approved and commercialised in Türkiye at the time of the study carried out using inductively coupled plasma MS (ICP-MS). Besides that, this study also aims to determine the heavy metal contamination in infant formulas (0–36 months; 8 Groups) in Türkiye, reveal if these samples meet the legal requirements, evaluate the exposure to toxic elements originating from the infant formulas and assess the potential health risks posed on the infants in Türkiye.

Materials and methods

Materials

In the present study, the presence and concentrations of heavy metals (As, Hg, Pb, Co, Cd, se, Cu, Zn, Sn and Al) in infant formulas and follow-on formulas were investigated. For this purpose, thirty-two infant formulas and forty follow-on formulas from different companies were used as study materials. The formulas examined include all of those available in Türkiye and the main brands are represented. The samples were kept in their original packages in a cool place until analysed in the laboratory. Table 1 shows the numbers and groups of samples used in analyses. Samples from different brands (sixteen brands), a total of seventy-two infant formulas (in powder form), in their original packages were purchased from a pharmacy. Heavy metal analysis was performed by using ICP-MS (Thermo Scientific™ iCAP) and Microwave Digestion System (Milestone Ethos Up). All the chemicals were at analytical reagent grade. Concentrated nitric acid (65 % HNO_3), hydrochloric acid (30 % HCl) and hydrogen peroxide were obtained from Sigma-Aldrich and Merck, respectively.

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Table 1. Infant formula sample characteristics (Numbers)

Samples	Age groups	*n*	Code number	Contains	Packaging
Infant formula	0–6 months	10	IF1	Cows' milk based	Metal container
Follow on milk	6–9 months	10	FM1	Cows' milk based	Paper and tin
Follow on milk	9–12 months	10	FM2	Cows' milk based	Paper and aluminium foil
Growing-up milk	12–36 months	10	GM	Cows' milk based	Paper and aluminium foil
Premature	0–6 months	8	P1	Cows' milk based	Metal container
Low birth weight	0–6 months	8	P2	Cows' milk based	Metal container
Hypoallergenic	0–6 months	8	H1	Goat's milk based	Metal container
Hypoallergenic	6–12 months	8	H2	Goat's milk based	Metal container
Total		72			

n, number of samples.

Determination of heavy metals

The method defined by Su *et al.* was used with slight modifications for the determination of the heavy metal analysis[30]. Before analysis, all quartz and nickel pieces in ICP-MS device were cleaned according to the cleaning procedure. The samples were prepared according to the 'baby food' method in the Food and Feed section of the Microwave Digestion System. 0·5 g was weighed from the samples and placed in Teflon cups. 9:1 ml HNO_3: H_2O_2 was added, and a closed system was set by enclosing all the Teflon cups in parts. The Teflon cups were pulled out at the end of 1 h. Once the infant formula solutions were cooled, they were put in 15 ml falcons, and the sample volume was completed to 15 ml by adding ultra-distilled water. Samples were filtered (0·22 μm) and analysed using ICP-MS. The analysis of the samples and blank test pieces was made by carrying out three parallel readings. The conditions of analysis are shown in Table 2.

Table 2. Inductively coupled plasma -MS parameters

RF power (W)	1548·6
Fogging	PFA-ST MicroFlow Nebuliser
Spray circle	Cyclonic Quartz
Argon plasma flow rate (l/min)	14
Auxiliary flow rate (l/min)	08021
Fogging gas flow rate (l/min)	0·8
Sample uptake/ml per min	0·5
Scanning mode	Peak hopping
Sampler and skimmer	Nickel
Dwell time (s)	0·01
The number of repetitions	3
Sampling depth (mm)	5
No. of sweeps	10
Time per sweep (s)	0·14
Time per main run (s)	1·4

Sample preparation for the device

In this process, 1 ml of sample was added with 10 ppb mix internal standard (Bi) (2 ppm Au standard was also added for Hg). The final volume was completed to 5 ml and the samples were diluted 100 times. Then, the elements in the samples were read using ICP-MS (Thermo Scientific) device at ppb level. Standard concentrations were 0·5, 1, 5, 10, 20, 50 and 100 ppb (Chem Lab Solutions). To provide the quality of measurements, recovery, instrument detection limits (LOD/LOQ) and calibration for all metals are shown in Table 3. Solutions (for standard) that were prepared by using stock solutions were recorded and the calibration curves were created (0·5, 1, 5, 10, 20, 50, 100 ppb). All heavy metal measurements were > 99·0 %. So, the method can be used in the analysis.

Risk assessment

The daily intake for each heavy metal analysed was estimated considering the concentration of the metal acquired from the analysis of the heavy metals, the average daily/weekly intake of the formula and the average body weight (bw) for girls and boys separately. Daily doses were computed using the babies' nutrition tables. The mean bw was defined according to the child-growth standard tables improved by WHO[31] considering the P95th percentile of the weight for girls and boys at 1st week; for the period of life of 0–2 weeks, 3rd week; for 2–4 weeks, 1st month; for 2 months, 4th month; for 4 months, 6–9 months, 9–12 months and 12–36 months. The daily/weekly intake for each heavy metal was calculated by the following equation:

Daily intake (μg/kg bw) = (Cm × EI)/bw

where Cm is the mean level of each heavy metal studied in the formulas, expressed as μg/g; EI is the daily/weekly estimated intake of formulas expressed as g and bw is the body weight expressed as kg.

The health risk index of heavy metals was calculated as a percentage of its safety limit. The safety limits were as follows: for Cd, the EFSA panel on contaminants in the food chain designates a PTWI of 2·5 μg/kg[32]; for Pb, the JECFA reports a PTWI equal to 3·5 μg/kg[33]; for Zn, the Scientific Committee on Food indicates a tolerable upper limit of 7 mg/d[34]; for Al, European Union commission limit of 2 mg/kg[35] (PTDI); for Mn, Codex Alimentarius Commission standard limit of 2·5 mg/kg PTWI[36]; for Co, maximum tolerable daily intake limit of 100 μg/kg bw[37]; for Cu, PTWI of 3·5 mg/kg[38]; for As, PTWI limit of 0·015 mg/kg[21]; for se, Sn and Hg, PTWI limits of 66 μg/kg, 0·6 mg/kg and 0·4 μg/kg, respectively[38,39].

Toxicological contribution

PTDI (EFSA and JECFA) contribution level of average exposure calculated for each heavy metal (% of PTDI) was calculated according to the formula[5].

% of PTDI = ((Mean estimated daily intake and P95th estimated daily intake) × 100]/PTDI

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Table 3. Analysis of the recovery, LOD and calibration for the heavy metals
(Means and standard deviations)

Element	Conc. (ppb)	%Recovery (mean)	Linear equation *x*, *y* (μg/l)	R^2	SD	RSD%	LOD (ppb)
^{27}Al	10	99·0	*y* = 13 972·2758*x* + 22 645·3554	0·9984	1·070	1·621	0·1434
^{55}Mn	10	99·0	*y* = 36 844·9564*x* + 7102·8305	0·9986	0·967	0·193	0·0377
^{59}Co	10	99·0	*y* = 29 016·7553*x* + 3706·7480	0·9987	0·920	0·128	0·0114
^{63}Cu	10	99·0	*y* = 15 417·0892*x* + 5664·2493	0·9994	0·639	0·367	0·0658
^{66}Zn	10	99·0	*y* = 5538·7939*x* + 4128·4920	0·9994	0·635	0·745	0·1155
^{75}As	10	99·0	*y* = 5569·6026*x* + 426·2260	0·9993	0·654	0·077	0·0413
^{77}Se	10	99·0	*y* = 331·8706*x* + 423·4978	0·9996	0·546	1·276	0·3157
^{111}Cd	10	99·0	*y* = 7693·8867*x* + 86·8002	0·9991	0·773	0·011	0·0100
^{118}Sn	10	99·0	*y* = 22 182·1770*x* + 1070·4592	0·9974	1·296	0·048	0·0252
^{208}Pb	10	99·0	*y* = 71 491·8714*x* + 5364·7357	0·9989	0·859	0·075	0·0051
^{202}Hg	1	99·0	*y* = 16 942·8985*x* + 119·8015	0·9978	0·628	0·007	0·0060

LOD, limit of detection; RSD, relative standard deviation.

Target hazard quotient is a risk index developed by the US Environmental Protection Agency to predict the relationship between exposure to chemical pollutants and potential health risks. While HI < 1 means that there is no concern about health risk, HI ≥ 1 indicates a potential health concern[40].

Results and Discussion

Infant formula samples from a total of sixteen brands (seventy-two samples; two batches of each brand) were analysed for Al, Mn, Co, Cu, Zn, As, se, Cd, Sn, Pb and Hg using ICP-MS. The mean levels of each heavy metal in the infant formula samples analysed are shown in Table 2. The mean Al levels of infant formula samples numbered Brand 9, 13 and 12 are 3·050 (SD 2·200), 3·044 (SD 1·266) and 2·576 (SD 0·707) μg/g, respectively (Table 4), and the average Al level for all samples is about 1·755 (SD 0·708) μg/g.

Comparing the groups (low birth weight, premature, hypoallergenic, follow-on milk, growing-up milk), the highest mean Al value was found to be 2·678 (SD 1·333) μg/g in the GM group (Brand 9), whereas the lowest one was found to be 0·551 (SD 0·212) μg/g in the premature group (Brand 2). Blasco and Golinda reported that an intermediate level was found for formulae without lactose and the lowest content was found in the hypoallergenic formula[22]. Comparing their results to the results achieved in the present study, the second-lowest Al value was found in the hypoallergenic group, following the premature group. In this study, the range of Al concentrations observed in infant formula (0·08–7·93 μg/g) is comparable to that reported in a study in the UK (0·69–5·27 μg/g)[41], higher than that in studies in Canada (0·018–1·10 μg/g)[42] and Pakistan (0·64–2·47 μg/g)[43], but lower than reported by Sipahi *et al.*[44] (2·40–34·6 μg/g).

The levels of Mn found in this study ranged between (0·242 and 20·828 μg/g) in the various brands of infant formula. The highest level of Mn was found in powdered infant formula (Brand 3) which was suitable for 9–12-month-old infants. All products satisfied national and Codex Alimentarius Commission international standards for minimum Mn level in infant formulas; however, 9/72 of the products purchased in the USA exceeded the Codex Alimentarius Commission guidance upper level of 100 μg Mn/kcal for infant formula. Frisbie *et al.* reported that the range of measured Mn concentrations in the products (infant formula and young child nutritional beverages) was 160–2800 μg/l[11]. In this study, 12·5 % (9 samples) of infant formula which is suitable for 9–12 months have Mn contents above the quantification limit.

The highest mean Pb concentrations of infant formula samples numbered Brand 13, Brand 2 and Brand 11 are 0·141 (SD 0·104), 0·140 (SD 0·110) and 0·126 (SD 0·018) μg/g, respectively, and the average Pb concentration for all samples was found to be approximately 0·071 (0·010–0·141) μg/g (Table 4). Various concentrations of Pb were defined in all infant formulas. The average Pb content is below (56 %; nine brands) the maximum limits (0·05 mg/kg) set by the European Union for infant formula[33], whereas all except only one brand (three samples) are above the maximum limits (0·01 mg/kg) set by the Codex Alimentarius Commission for infant formulas[36] (Fig. 1).

Nonetheless, the highest Pb content was found in the milk-based 'beginner' formula (0–6 month, IF1) packaged in metal containers. In addition, only one batch per brand contained detectable levels of Pb. This may be attributed to differences in the quality of raw materials, production and processing equipment and packaging containers used by infant formula manufacturers. The examined range of Pb level is considerably greater than that reported for analogous studies in Türkiye[44] (0·55–24·9 μg/kg) and Ethiopia[45] (16·0–103 μg/kg) but less than the range observed in Egypt[46] (450–1850 μg/kg) and Lebanese[47] (31·0–1040 μg/kg).

Evaluating the Cd results, it was determined that Cd could not be detected in one sample (Brand 11) (Fig. 1), while it was below the limit values in thirteen brands (sixty-one samples; 85 %).

Cd level exceeded the limit values in all infant formulas Brand 3 (0·038 μg/g) and Brand 15 (0·023 μg/g) (Table 4). It was determined that the Cd level exceeded the limit values in a total of 9 (12·5 %) samples. The levels detected are above the Cd concentrations (0·005–0·02 mg/kg) determined by the European Union for infant formulas[48]. In addition, European Union No 488/2014 amending the Regulation (EC) No 1881/2006 sets a maximum limit of 0·01 mg/kg fresh weight for powdered infant formula made from protein obtained from cow milk or from protein

Table 4. Heavy metal contents in different types of commercially available infant formulas in the Turkish market
(Mean values and standard deviations)

µg/g	^{27}Al		^{55}Mn		^{59}Co		^{63}Cu		^{66}Zn		^{75}As		^{77}Se		^{111}Cd		^{118}Sn		^{208}Pb			^{202}Hg		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	^{209}Bi %*	Mean	SD	^{209}Bi %*
Brand 1	2·113–1·124		1·357–0·259		0·006–0·004		2·637–1·928		35·893–22·209		0·776–0·318		0·386–0·242		0·012–0·004		0·000–0·000		0·061–0·003		112·505	0·016–0·003		100·810
	1·356	0·339	0·737	0·480	0·005	0·001	2·305	0·258	26·475	5·577	0·426	0·159	0·332	0·057	0·007	0·004	0·000	0·000	0·026	0·018		0·008	0·004	
Brand 2	1.405-0.551		0.335-0.164		0.006-0.001		2.140-0.970		22.377-9.106		1.380-0.280		0.311-0.163		0.010-0.000		0.000-0.000		0.330-0.050		105·590	0·020–0·000		103·560
	1·086	0·348	0·242	0·066	0·004	0·002	1·536	0·427	16·366	5·507	0·520	0·480	0·257	0·060	0·010	0·000	0·000	0·000	0·140	0·110		0·010	0·001	
Brand 3	3·976–1·687		25·895–17·847		0·053–0·028		4·006–1·142		81·277–63·427		1·149–0·749		0·228–0·151		0·046–0·031		0·000–0·000		0·221–0·039		115·837	0·006–0·000		103·155
	2·394	0·835	20·828	2·714	0·038	0·009	2·174	1·063	69·179	6·617	0·931	0·162	0·192	0·028	0·038	0·005	0·000	0·000	0·109	0·078		0·004	0·002	
Brand 4	1·707–1·021		0·416–0·205		0·016–0·005		1·952–1·419		19·111–15·108		0·341–0·245		0·227–0·154		0·014–0·001		0·736–0·000		0·075–0·015		107·416	0·019–0·007		102·938
	1·378	0·279	0·268	0·086	0·008	0·005	1·558	0·223	16·148	1·681	0·293	0·043	0·181	0·030	0·008	0·005	0·089	0·362	0·042	0·025		0·013	0·005	
Brand 5	1·707–1·082		0·577–0·205		0·016–0·005		2·177–1·137		23·071–14·606		0·511–0·245		0·407–0·154		0·009–0·001		0·000–0·000		0·075–0·003		107·819	0·017–0·005		99·919
	1·286	0·251	0·393	0·151	0·010	0·005	1·534	0·345	17·323	3·530	0·342	0·112	0·256	0·114	0·005	0·003	0·000	0·000	0·039	0·030		0·010	0·004	
Brand 6	1·951–0·833		1·863–0·267		0·011–0·003		2·386–1·283		31·264–14·096		0·414–0·253		0·339–0·185		0·016–0·000		0·000–0·000		0·187–0·014		112·137	0·013–0·004		100·143
	1·428	0·366	0·739	0·102	0·006	0·002	1·980	0·542	22·054	1·137	0·324	0·037	0·250	0·117	0·007	0·004	0·000	0·000	0·047	0·024		0·007	0·006	
Brand 7	1·362–0·551		0·398–0·161		0·007–0·002		0·208–0·834		21·708–19·188		0·033–0·0251		0·456–0·189		0·010–0·000		0·000–0·000		0·054–0·001		105·586	0·018	0·004	100·882
	0·823	0·365	0·253	0·101	0·004	0·002	0·144	0·541	20·099	1·137	0·029	0·003	0·287	0·116	0·006	0·004	0·000	0·000	0·032	0·024		0·011	0·006	
Brand 8	1·072–0·750		0·398–0·234		0·005–0·003		2·149–0·609		22·145–17·305		0·452–0·218		0·299–0·185		0·027–0·001		0·000–0·000		0·035–0·015		113·148	0·013–0·002		103·276
	0·911	0·147	0·287	0·075	0·004	0·001	1·325	0·781	19·259	2·075	0·337	0·103	0·233	0·051	0·012	0·012	0·000	0·000	0·024	0·009		0·007	0·006	
Brand 9	5·583–1·622		1·266–0·308		0·088–0·003		2·534–1·708		50·318–24·012		0·600–0·323		0·471–0·190		0·009–0·000		0·000–0·000		0·062–0·031		100·817	0·026–0·009		106·415
	3·050	2·200	0·671	0·519	0·032	0·048	2·073	0·421	35·170	13·600	0·456	0·139	0·296	0·153	0·005	0·004	0·000	0·000	0·044	0·016		0·015	0·009	
Brand 10	2·168–1·570		2·014–0·305		0·008–0·004		2·442–1·684		32·579–20·062		3·585–0·433		0·388–0·231		0·015–0·006		0·062–0·000		0·273–0·000		111·816	0·027–0·001		104·552
	1·804	0·247	0·742	0·721	0·006	0·002	1·934	0·312	23·233	5·252	1·080	1·041	0·295	0·071	0·010	0·004	0·000	0·000	0·119	0·109		0·008	0·011	
Brand 11	2·057–1·406		0·316–0·292		0·011–0·005		0·666–0·638		29·420–17·397		0·397–0·286		0·218–0·153		0·001–0·000		0·000–0·000		0·139–0·114		109·282	0·008–0·004		102·480
	1·731	0·461	0·304	0·017	0·008	0·004	0·652	0·020	23·409	8·501	0·341	0·079	0·186	0·046	0·001–0·000		0·000–0·000		0·126–0·018			0·006–0·003		
Brand 12	3·334–1·859		21·223–0·181		0·032–0·003		2·400–0·492		66·758–9·607		0·767–0·273		0·235–0·181		0·034–0·000		0·000–0·000		0·221–0·008		109·325	0·010–0·000		102·861
	2·576	0·707	4·747	9·237	0·009	0·013	1·346	0·694	25·128	23·829	0·419	0·200	0·207	0·024	0·010	0·014	0·000	0·000	0·122	0·076		0·007	0·004	
Brand 13	4·503–2·229		2·443–0·819		0·032–0·009		2·108–0·977		35·486–31·360		0·782–0·384		0·348–0·259		0·014–0·001		0·000–0·000		0·257–0·058		106·194	0·010–0·003		102·010
	3·044	1·266	1·595	0·815	0·017	0·013	1·370	0·640	33·068	2·152	0·523	0·225	0·317	0·051	0·005	0·008	0·000	0·000	0·141	0·104		0·006	0·003	
Brand 14	2·730–1·067		1·806–0·259		0·006–0·004		3·115–1·138		32·732–24·999		0·776–0·318		0·560–0·242		0·012–0·004		0·000–0·000		0·080–0·019		107·179	0·016–0·003		100·810
	1·477	0·705	0·986	0·680	0·005	0·001	2·121	0·728	28·763	3·530	0·452	0·189	0·341	0·125	0·007	0·004	0·000	0·000	0·045	0·025		0·008	0·005	
Brand 15	3·637–1·241		25·631–0·201		0·060–0·001		2·611–1·182		88·707–16·910		2·542–0·274		0·386–0·256		0·053–0·003		0·000–0·000		0·041–0·009		101·928	0·013–0·005		102·302
	2·284	1·228	8·699	1·466	0·022	0·003	1·909	0·715	42·972	39·737	1·325	1·143	0·314	0·066	0·023	0·026	0·000	0·000	0·010	0·027		0·008	0·004	
Brand 16	2·557–0·814		2·098–0·330		0·017–0·002		2·255–1·127		43·832–12·633		0·453–0·271		0·473–0·259		0·008–0·001		0·000–0·000		0·266–0·014		100·492	0·010–0·003		100·742
	1·457	0·751	0·971	0·689	0·009	0·006	1·489	0·441	29·514	12·490	0·392	0·071	0·346	0·083	0·004	0·004	0·000	0·000	0·075	0·107		0·007	0·003	

* Internal standard ^{209}B.

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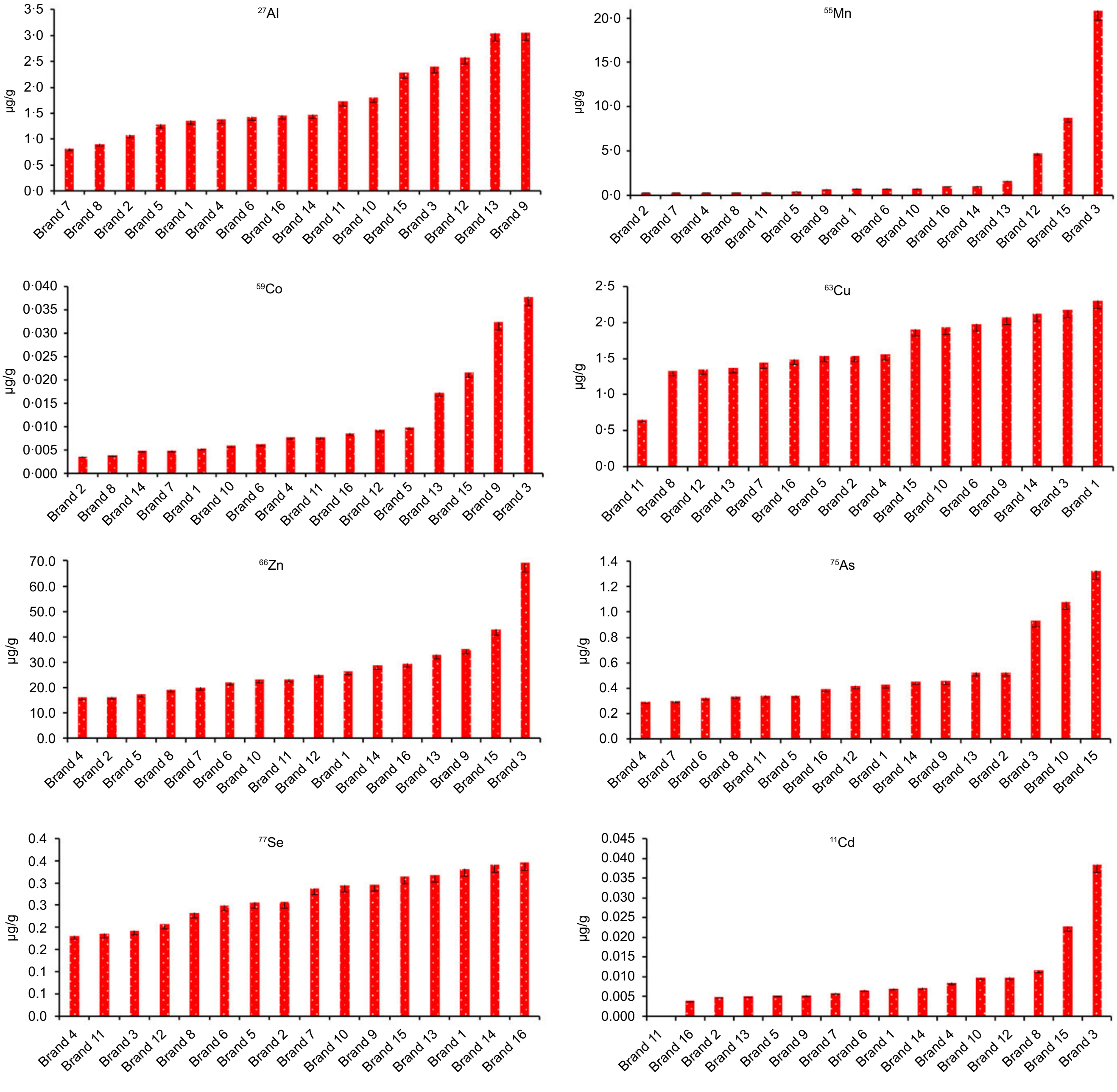

Fig. 1. Heavy metal levels of all brands (average of all groups).

hydrolysates, and of 0·02 mg/kg fresh weight for infant formula prepared from soya protein either alone or in combination with cow milk[49]. Therefore, the mean Cd concentration found reaches the maximum limit established in the legislation.

As can cause cancer in many organs, including the skin, lungs, bladder, kidney and liver; it is also capable of influencing the neurological, respiratory and cardiovascular systems. As has also been implicated in diabetic pathophysiology and reproductive toxicity[50]. Recent research showed that infant formulas, specifically rice-based infant food, contain As which can be traced to the natural raw materials used for processing[51]. Currently, there is no guideline for As content in baby food, including infant formulas, but the food industry has been advised to adhere to a 0·2 mg/kg As level to ensure the safety of infants and young children[52]. In the present study, the highest mean As level in infant formula samples numbered Brand 15, Brand 10 and Brand 3 was 1·325, 1·080 and 0·931 mg/kg, respectively, and the average As concentration for all analyses was found to be approximately 0·529 mg/kg (Table 4). In intergroup comparison, the lowest As level was found to be in hypoallergenic group (0·218 (SD 0·057) mg/kg), whereas the highest one was found in follow-on formula (9–12 months).

The mean Hg l concentration of all formulas was approximately 0·0086 (SD 0·003) (0·0035–0·0155) mg/kg (Table 4). When the detections were compared with other studies, it was found that there were studies reporting lower levels at

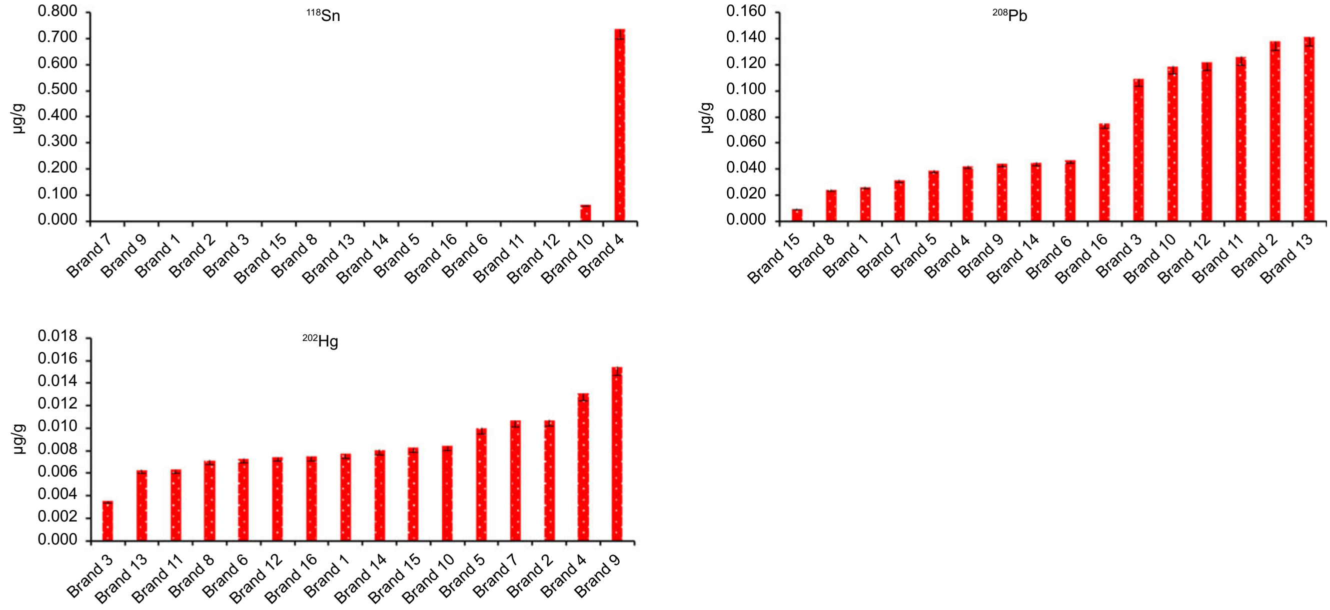

Fig. 1. (Continued)

0·009–0·031 mg/kg[20], 0·006–0·007 mg/kg[53] and higher levels at 0·02–1·56 mg/kg[54], 0·012–0·251 mg/kg[47]. The mean Hg level of all analyses was approximately 0·0086 (SD 0·003) (0·0035–0·0155) µg/g (Table 4). The lowest Hg level was found in the premature group and the highest Hg concentration was found in the growing-up formula group. There is no limitation for Hg concentration in infant formulas. Hg concentrations in infant formulas were recorded to be 0·0005 mg/kg by Martins *et al.*[55], 0·0007 mg/kg by Mania *et al.*[12], 0·0000–0·0005 by Guerin *et al.*[56], 0·03 mg/kg by Martínez *et al.*[57] and 0·01 mg/kg by Igweze *et al.*[54].

Examining the Sn levels, no Sn was detected in fourteen brands but only in two brands. Sn levels in Brand 4 and Brand 10 (0·089 (SD 0·004); 0·062 (SD 0·002) mg/kg) were much lower than the level set by EFSA and they constituted 3 % (2 samples) of all the samples. Sn is one of the toxic metals, which could accumulate in the human body and animal tissues. Sn is widely used in Sn-plated steel containers, which are used for food production and preservation of beverage cans. In case of exposure to a large amount of Sn in canned food taken daily over a long period, acute effects such as stomach aches and anaemia occur in liver and kidney[58,59]. The permissible limit for Sn in infant formula is 50 mg/kg[60].

Comparing the Cu values of all infant formulas, Cu was detected in all of them. The highest value among the brands was found in Brand 1 (9–12 months, seven samples) and found to be 2·637 (SD 1·062). This value is much higher than the reference values set in the national and international standards. It was thought that this might be because of the package of product. In other studies, Cu values were reported to exceed the limit values to varying extents[58].

Zn is a minor inorganic compound essential for the growth of infants. Zn is also required for the synthesis of DNA, division of cells and catalytic activity of more than 100 enzymes[61]. This study disclosed that the levels of Zn in infant formulas ranged between 16·148 and 69·179 µg/g (Table 4). According to Türkiye and international standards, the Zn content in infant formulas must not exceed < 36 mg/kg[62,63]. Comparing this limit with our results, two brands were found exceeding the permissible limit. Level of Zn recorded from Pakistani in thirteen different brands of infant formulas ranged between 29·72 and 113·50 mg/kg, and these results are higher as compared with our findings[64]. The level of Zn recorded by Melø *et al.*[65] in samples present in Norway markets was in the range of 35·0–39·0 mg/kg and these results are lower as compared with our evidences.

Estimated daily intake

The concentrations of the daily/weekly intake of non-essential and toxic elements and micro and trace essential elements calculated separately for girls and boys are reported in Table 5. The advised consumption and the average concentrations acquired for each heavy metal were taken into account to calculate the estimated daily intake, as well as metals' contribution to the proposed daily intake and the maximum intake for the infant formulas (Table 5). The levels of toxic contribution of the analysed exposure for each heavy metals to PTDI (% of PTDI) defined by JECFA are shown in Table 5.

The toxicity of As varies depending on As' forms, and it is known that inorganic As is more toxic than organic As. Different studies examining the infant formulas with different contents reported that approximately 50–80 % of total As was in iAs form[66–68]. When the findings of this study are evaluated, As exposures of all groups were calculated as approximately 0·24, 0·40, 0·72, 0·66 and 0·38 µg/kg bw/d.

Food safety authorities defined the daily iAs values to be 0·3–8 µg/kg bw/d for liver, skin and some cancer types[69]. The analysed average As exposure was below the levels defined by EFSA and JECFA. The average Cd exposure of infants 6–9 months is 0·013 (SD 0·001) µg/kg bw/d (P95, 0·03235 µg/kg bw/d), and

Table 5. Daily/weekly intake of metals and percentage (P95th) health risk index estimated for infants from each group, separately for girls and boys

	^{27}Al		^{55}Mn		^{59}Co		^{63}Cu		^{66}Zn		^{75}As		^{77}Se		^{111}Cd		^{118}Sn		^{208}Pb		^{202}Hg	
EDI	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys
0–2 weeks	0·20	0·19	0·68	0·65	0·0113	0·0107	4·01	3·82	48·95	46·62	0·75	0·72	0·65	0·62	0·0135	0·0129	ND		0·0653	0·0621	0·023	0·021
2–4 weeks	0·23	0·22	0·78	0·74	0·0130	0·0123	3·58	3·39	56·48	53·40	0·87	0·82	0·76	0·71	0·0156	0·0147			0·0753	0·0712	0·026	0·025
2 months	4·63	4·29	5·66	5·24	0·0314	0·0291	4·97	4·61	74·66	69·17	1·31	1·22	0·74	0·69	0·0229	0·0212			0·2000	0·1853	0·029	0·026
4 months	3·99	3·75	10·65	10·02	0·0313	0·0295	4·96	4·66	82·88	77·95	1·22	1·15	0·74	0·70	0·0285	0·0268			0·2563	0·2411	0·028	0·027
6–9 months	4·72	4·23	12·99	11·64	0·0313	0·0280	5·31	4·76	93·79	84·06	2·27	2·04	0·74	0·66	0·0341	0·0306			0·2274	0·2038	0·028	0·025
9–12 months	5·94	5·64	8·73	8·30	0·0330	0·0314	5·73	5·44	81·24	77·20	2·04	1·94	0·81	0·77	0·0300	0·0285	2·21	2·10	0·2400	0·2281	0·030	0·029
1–3 years	6·13	5·74	10·60	9·92	0·0458	0·0429	4·33	4·05	75·94	71·10	1·17	1·09	0·62	0·58	0·0320	0·0300	0·14	0·06	0·1602	0·1500	0·023	0·021
	^{27}Al		^{55}Mn		^{59}Co		^{63}Cu		^{66}Zn		^{75}As		^{77}Se		^{111}Cd		^{118}Sn		^{208}Pb		^{202}Hg	
PTWI or PTDI*	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys
0–2 weeks	0·01	0·01	0·27	0·26	0·0001	0·0001	1·15	1·09	6·99	6·66	0·251	0·239	0·010	0·009	0·005	0·005	0·00	0·00	0·0186	0·0178	0·006	0·005
2–4 weeks	0·01	0·01	0·31	0·30	0·0001	0·0001	1·02	0·97	8·07	7·63	0·289	0·273	0·011	0·011	0·006	0·006	0·00	0·00	0·0215	0·0203	0·006	0·006
2 months	0·15	0·14	2·26	2·10	0·0003	0·0003	1·42	1·32	10·67	9·88	0·438	0·406	0·011	0·010	0·009	0·008	0·00	0·00	0·0571	0·0529	0·007	0·007
4 months	0·13	0·13	4·26	4·01	0·0003	0·0003	1·42	1·33	11·84	11·14	0·408	0·384	0·011	0·011	0·011	0·011	0·00	0·00	0·0732	0·0689	0·007	0·007
6–9 months	0·16	0·14	5·20	4·66	0·0003	0·0003	1·52	1·36	13·40	12·01	0·758	0·679	0·011	0·010	0·014	0·012	0·00	0·00	0·0650	0·0582	0·007	0·006
9–12 months	0·20	0·19	3·49	3·32	0·0003	0·0003	1·64	1·56	11·61	11·03	0·680	0·646	0·012	0·012	0·012	0·011	3·68	3·50	0·0686	0·0652	0·008	0·007
1–3 years	0·20	0·19	4·24	3·97	0·0005	0·0004	1·24	1·16	10·85	10·16	0·389	0·364	0·009	0·009	0·013	0·012	0·24	0·11	0·0458	0·0429	0·006	0·005
Toxicological contribution (%)	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
0–2 weeks	0·07	0·06	2·72	2·59	0·00	0·00	11·46	10·91	6·99	6·66	2·51	2·39	0·10	0·09	0·05	0·05	0·00	0·00	0·19	0·18	0·06	0·05
2–4 weeks	0·08	0·07	3·14	2·97	0·00	0·00	10·24	9·68	8·07	7·63	2·89	2·73	0·11	0·11	0·06	0·06	0·00	0·00	0·22	0·20	0·06	0·06
2 months	1·54	1·43	22·63	20·96	0·00	0·00	14·20	13·16	10·67	9·88	4·38	4·06	0·11	0·10	0·09	0·08	0·00	0·00	0·57	0·53	0·07	0·07
4 months	1·33	1·25	42·61	40·07	0·00	0·00	14·16	13·32	11·84	11·14	4·08	3·84	0·11	0·11	0·11	0·11	0·00	0·00	0·73	0·69	0·07	0·07
6–9 months	1·57	1·41	51·95	46·56	0·00	0·00	15·18	13·61	13·40	12·01	7·58	6·79	0·11	0·10	0·14	0·12	0·00	0·00	0·65	0·58	0·07	0·06
9–12 months	1·98	1·88	34·92	33·18	0·00	0·00	16·37	15·56	11·61	11·03	6·80	6·46	0·12	0·12	0·12	0·11	36·80	34·97	0·69	0·65	0·08	0·07
1–3 years	2·04	1·91	42·39	39·69	0·00	0·00	12·36	11·57	10·85	10·16	3·89	3·64	0·09	0·09	0·13	0·12	2·36	1·07	0·46	0·43	0·06	0·05
TOXIC THQ < 1	0–2 weeks	2–4 weeks	2 months	4 months	6–9 months	9–12 months	1–3 years															
	0·01	0·01	0·04	0·04	0·05	0·77	0·09															

ND, not detected; EDI, estimated daily intake; PTWI, provisional tolerable weekly intake; PTDI, provisional tolerable daily intake; THQ, target hazard quotient.
* Cu, Pb, Mn, Cu, As, se, Sn and Hg for PTWI; Zn, Al and Co for PTDI.

the analysed exposure level corresponds to 1·2 % of PTWI and 8·98 % of PTDI (Table 5). EFSA defines that tolerable daily intake for Cd was 0·36 µg/kg bw/d (2·5 µg/kg bw/week) for 0–24 months[17], while JECFA specified it to be 1 µg/kg bw/d (7 µg/kg bw/week)[60]. The average and highest (P95) Cd exposures analysed were below the levels stated by EFSA and JECFA.

The mean Hg exposure of the infant group of 9–12 months was analysed as 0·007 (SD 0·001) µg/kg bw/d (P95, 0·030 µg/kg bw/d) (Table 5). The exposure level analysed was 0·731 % of PTDI. JECFA defined to be PTDI 0·570 µg/kg bw/d (4·0 µg/kg bw/week) for iHg[60], and EFSA defined to be 0·180 µg/kg bw/d (1·3 µg/kg bw/week) for met-Hg[20]. The analysed average and highest (P95) Hg exposure is quite under the levels stated by EFSA and JECFA.

The lowest (P95, 0·017 µg/kg bw/d) and highest (P95, 0·073 µg/kg bw/d) exposure levels recorded were 4·8 (SD 0·20) % of PTDI (mean) (Table 5). The average Pb exposure values analysed in different studies were 0·50 µg/kg bw/d and 3·57 µg/kg bw/d (25 µg/kg bw/week)[5], and levels were below the one defined by EFSA for developmental neurotoxicity in young children[33].

JECFA interpreted present values for Al 11 years ago[60]. The authorities made a decision that a 'No Observed Adverse Effect Level' of 30 mg/kg bw/d was suitable for establishing a PTWI for Al compounds. Because long-term studies on the relevant toxicological endpoints had become present, there was no longer the requirement for an additional indefiniteness factor for insufficiencies in the database. The authorities, therefore, determined a PTWI of 2 mg/kg bw/week from the NOAEL of 30 mg/kg bw/d by performing an indefiniteness factor of 100 for inter-species and intra-species differences.

Conclusions

It was reported that newborns are more likely to be exposed to higher levels of metals through infant formula when compared with breast milk. This fact is important to reduce health risks by imposing a set of maximum permissible concentrations for all toxic compounds in baby foods in the practicable legislations, particularly in foodstuffs that include higher toxic metals contamination. Furthermore, considering that newborns who cannot be breastfed are particularly dependent on formula diets and that infants are potentially more sensitive, heavy metal contamination and essential metal limits should be regularly monitored during manufacturing. Taking dairy products' importance into account in terms of public health, as well as the relationship between the food quality and the health of the population, the systematic surveillance of high heavy metals contamination levels in these products must be considered in food quality control policies in Türkiye.

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T. D. and S. A. conceived and designed the research. T. D. conducted the experiments, and S. A. contributed to biochemical analyses. T. D. analysed the data and wrote the first manuscript draft, T. D. and S. A. revised the paper up to its final version. All authors have read and agreed to the published version of the manuscript.

The authors declare no conflict of interest.

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