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The analysis of Cu, Mn and Zn content in prescription food for special medical purposes and modified milk products for newborns and infants available in Polish pharmacies from toxicological and nutritional point of view

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ABSTRACT

Background: Prescription food for special medical purposes (FSMPs) and modified milk products (MMPs), available in pharmacies, are important for newborns and infants that are not breastfed. In the scientific literature there is a lack of comprehensive studies and corresponding safety assessment of the essential trace elements in these products.
Objective: The aim of this article was determination of Cu, Mn and Zn levels in the most frequently available prescription FSMPs (n = 6) and MMPs (n = 6) available in Polish pharmacies.
Methods: Flame absorption spectrometry (FAAS) following microwave induced digestion (concentrated nitric acid) was applied to determine the levels of the elements in the products.
Results: Our studies are based on a triple approach (1) the "*raw results*" of Cu, Mn and Zn levels (products in powdered form), (2) *single intake* - the level of each essential trace element consumed in one portion, (3) the *daily intake* depending on age and weight including comparison with Adequate Intake established by European Food Safety Authority.
Conclusion: The results show the occurrence of differences between the manufacturer's declared composition and the finished product for consumption. The prescription FSMPs in comparison to MMPs available in Polish pharmacies contain similar levels of Cu, Mn and Zn. Our results show additionally that all of the products do not represent a health hazard to the newborns and infants. This is a pioneer study in terms of the safety assessment, and quality of prescription FSMPs and MMPs available in Polish pharmacies from toxicological and nutritional point of view.

1. Introduction

During the infancy period, breast milk, prescription food for special medical purposes (FSMPs) and modified milk products (MMPs) available in pharmacies and markets are the major source of essential trace elements for infants [1]. Despite the fact that the World Health Organization (WHO) recommends breastfeeding as the best feeding choice [2], prescription FSMPs and also MMPs available in pharmacies are a common alternative to breastfeeding. It should be emphasised that this alternative is sometimes a choice dictated by several types of allergies, diseases and/or dietary problems. Moreover, there are also other issues related to this possibility. For example, as was described by the Polish Center for Lactation Science, in Poland mothers want to feed their babies naturally – c.a. 98% of mothers begin to breastfeed their babies after childbirth. However, the number of breastfeeding mothers drops drastically to 46% in the first month after the birth of a baby [3].

Abbreviations: AI, Adequate Intake; Ars, Average Requirements (ARs); F AAS, flame atomic absorption spectrometry technique; Bw, body weight; EFSA, European Food Safety Authority; EU, European Union; FCS, food contact substance; FSMPs, food for special medical purposes; IOM, Institute of Medicine; MMPs, modified milk products; n/a, not available; PRIs, Population Reference Intakes; WHO, World Health Organization; SD, tandard deviation

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Products available from pharmacies seem to be the most appropriate formulations with which to follow on from breast feeding. However, there is a lack of studies around the safety and quality of prescription FSMPs and MMPs available in pharmacies, with appropriate toxicological analysis.

It is well known that adequate levels of essential trace elements in the diet of babies in the infancy period are essential for lifelong health and well-being. This is due to the fact that this period is characterised by a very high growth rate and microelemental requirements are more critical than in the later stages of growth [4]. It should be noted that essential trace elements are necessary for many various functions in the body, especially bone mineralization, enzymatic reactions and protection of cells and lipids in biological membranes. Toxicological aspects related to this topic are consequences of especially (1) low intake or reduced bioavailability of essential trace elements which causes impairment of body functions and (2) excessive levels associated with important potential toxic effects [5]. Unfortunately, essential trace elements present in prescription FSMPs and MMPs available in pharmacies have received little attention or only limited toxicological consideration.

Cu, Mn and Zn are major essential trace elements and have different and important biochemical functions in living organisms. Cu can be classified as a major essential trace element due to the wide range of enzymes that use this element as a co-factor. Hence, the symptoms of Cu deficiency are diverse [6], for example, scoliosis and scorbutic-like changes have been reported in copper-deficient infants and children [7]. On the other hand, an excess of this element has been recorded and shown to cause problems only under certain conditions, notably genetic disorders such as Wilson disease [8].

Mn is also a major essential trace element because this element is an essential dietary mineral for mammals. It is a component of metalloenzymes such as superoxide dismutase, arginase and pyruvate carboxylase, and is involved in amino acid, lipid and carbohydrate metabolism [9]. The evidence of Mn deficiency in newborns and infants is poor – a specific deficiency syndrome has not been described in humans [10]. Hence, Mn deficiency is an important problem, but also important is an excess of this element. The symptoms of Mn toxicity can result in a permanent neurological disorder known as manganism [11]. Furthermore, oral exposure to manganese can also cause adverse health effects, which are similar to those observed by inhalation exposure [11]. It should also be noted thatthe level at which exposure to Mn is related to any toxicological effects has not been established especially for newborns and infants [11].

Undoubtedly, Zn is ubiquitous and one of the essential trace elements. This element takes part in many physiological functions and is ubiquitous within every cell in the body [12]. This is the reason why Zn deficiency is very important topic. On the other hand, chronicly high Zn intake can result in different diseases like copper deficiency as the results of antagonism of both elements [13].

There is no doubt that safety assessment of trace elements and control studies about metallic impurities in milk-based products for babies are very important. In the scientific literature articles about determination of trace elements in milk-based products are very common, however most of investigated products are available in markets and approaches in safety assessment are insufficient. Hence, the justifications for undertaking the analysis of Cu, Mn and Zn content in prescription FSMPs and MMPs available in pharmacies for newborns and infants available in Polish pharmacies are (1) lack of studies about safety assessment of FSMPs and MMPs from pharmacies, (2) insufficient approaches in safety assessment, (3) lack of interpretation of obtained results from toxicological and nutritional point of view and (4) inadequate sensitivity and validation of the applied analytical technique.

The analysis of these products requires the application of sensitive, selective and validated analytical techniques. In scientific articles about analysis of trace elements in milk-based products for babies, different analytical techniques are applied. However only three are commonly applied - (1) neutron activation analysis (NAA), (2) inductively coupled plasma mass spectrometry (ICP-MS) and the most common technique – (3) atomic absorption spectrometry (AAS). It is worth noting that high-resolution continuum source atomic absorption spectroscopy (HR-CS AAS) appears to be a good alternative for the determination of heavy metallic elements according to traditional AAS. However, in these studies we applied the well-known and accepted AAS technique with flame atomisation (F-AAS) due to its simplicity, availability and well-grounded analytical background.

Hence, the aim of our article was the analysis of Cu, Mn and Zn content in prescription FSMPs ($n = 6$) and MMPs available in Polish pharmacies ($n = 6$) from a toxicological and dietary point of view.

2. Material and methods

2.1. Reagents and materials

In the preparation of all sample solutions, demineralized water (Millipore) and suprapure nitric acid (65%) at spectroscopic grade Merck (SupraPur, Darmstadt, Germany) were used. To avoid any metallic impurities/contamination at all stages of our study, all plastic and glass materials and equipment were previously treated in 0.5 mol/L nitric acid for 24 h and then rinsed using demineralized water. Certified standard solutions (1000 µg/L, Merck; for each element) and demineralized water were used for preparation of standard solutions. Acetylene (99.99%) was used in the atomization technique. Corn Flour, INCT-CF-3 (the Institute of Nuclear Chemistry and Technology Department of Analytical Chemistry) was used as the certified reference material (CRM). Additional information about the reference material is described in the supporting information (see Table S1).

2.2. Samples

2.2.1. Description of samples

The twelve different pharmaceutical products, i.e. prescription FSMPs ($n = 6$) and MMPs ($n = 6$) were obtained in pharmacies in Poland (Kraków and Niepołomice). The choice of products was based on their availability in Polish pharmacies. Our research includes all of the products issued on prescription and available in Polish pharmacies since January 2019. It should be noted that our studies include only products available in pharmacies but not in markets, hence sample size cannot be extended. Based on our best knowledge this situation is very similar in other countries in European Union. The products dedicated to babies at 0–6 months (initial milk formulas) were numbered as “1”. Similarly, the products dedicated to babies at 7–12 months (subsequent milk formulas) from the same manufacturer were numbered as “2”. Hence, twelve products – six FSMPs (A1, A2, B1, B2, C1 and C2) and six MMPs (D1, D2, E1, E2, F1 and F2) dedicated for newborns and infants were analysed. The coding system of samples is given in the supporting information (see Table S2). The manufacturer’s declared level of analysed essential trace elements of each sample is shown in the supporting information (see Table S3).

2.2.2. Sampling

A representative amount from the original packaging of each FSMP or MMPs was collected. The sampling procedure was carried out using a single plastic spoon added to the product to avoid any possible metallic impurities. All samples were stored at room temperature in sterilised disposable containers made of plastic (containers for urine analysis from pharmacies).

2.2.3. Pre-treatment of samples

Prior to the measurements, samples were dried in an oven at 70 °C in a ceramic crucible, of known weight, for 48 h. Weight consistency was checked after drying. The moisture content of the products under test (calculated from the mass difference prior to and after drying) was about 2.5%.

2.3. Apparatus and applied methods

All instrumental parameters are presented in the sections below and more details are described in the supplementary materials mentioned in

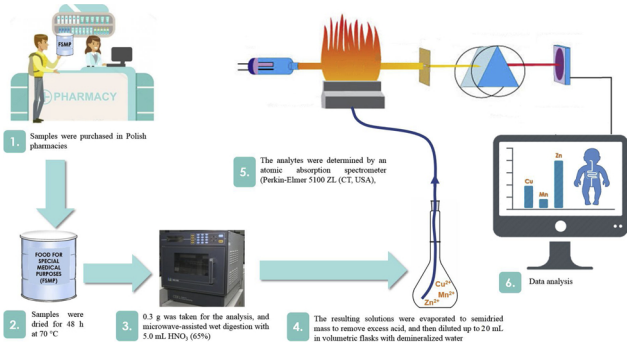

Fig. 1. The basic workflow of the analysis of Cu, Mn and Zn in prescription FSMPs and modified milk products for babies in infancy period by the F AAS.

the text. For better readability, the simplified workflow of analysis steps is illustrated in Fig. 1.

2.3.1. Digestion

A microwave-assisted digestion procedure was applied in order to achieve a shorter digestion time. A microwave oven MDS 2000 (CEM USA) programmable for time and microwave power was applied. Approximately 300 mg of each sample was placed in microwave-assisted wet digestion vessels with 5.0 mL of nitric acid. The digestion step lasted about 0.5 h. The multi-stage digestion program is presented in the supporting information (see Table S4). After cooling, the resulting solutions (digests) were evaporated to semidried mass to remove excess acid, and then diluted up to 20 mL in volumetric flasks using demineralized water and kept as stock sample solutions. The sample solutions were stored at room temperature (20–22 °C) until determination of the metals.

2.3.2. Determination of Cu, Mn and Zn

All analyses were performed using a Perkin-Elmer 5100 ZL (CT, USA) atomic absorption spectrometer (AAS) with Zeeman background correction and with flame atomization (FA). Deuterium lamp background correction (Perkin-Elmer 5100 ZL, CT, USA) was applied. The important instrumental parameters are presented in the supporting information (see Table S5).

2.3.3. Analytical calibration and quality control

The linear range of the calibration curve reached from the detection limit up 0.0; 0.25; 0.5; 1.0; 2.0; 3.0 mg/L for Cu, 0.0; 0.25; 0.5; 1.0; 2.0; 5.0 mg/L for Mn, and 0.0; 0.25; 0.5; 1.0; 2.0; 3.0 for Zn mg/L, respectively. A good indicator of the linearity for AAS instrument for precision and accuracy of results is the correlation coefficient (R) [14]; all obtained R values were acceptable, i.e. ≥ 0.998 (0.998 for Cu, 0.999 for Mn and 0.998 for Zn).

The LODs were determined for Cu, Mn and Zn as 2.1 µg/L, 3.2 µg/L and 2.0 µg/L, respectively. The recoveries obtained were 96.8.0% for Cu, 98.2% for Mn and 97.6% for Zn. The recoveries were calculated as the quotient of the determined level and the known amount of the determined element expressed as a percentage.

Blank samples of ultrapure water were prepared to apply the same procedure as for the samples to assess possible impurities during sample preparation and analytical calibration step. All blanks contained negligible amounts of Cu, Mn and Zn. Newly prepared standard stock solutions were serially diluted and applied to obtain calibration functions.

The confirmation of the quality control and validation of the applied methodology are previously described using the same methodology and apparatus – Cu [15], Mn [16] and Zn [17].

2.3.4. Statistical analysis

All measurements were performed in three replications. The mean, standard deviation (SD) and further calculations were made using Microsoft Office Excel 2016 for Windows.

3. Results

The Cu, Mn and Zn concentrations in the samples can be presented considering three approaches (1) the "raw results" - results of the dry weight, (2) values for one-time administration - including dilution in the finished product, (3) and the daily dose. This proposed approach is appropriate because it includes (1) *information about the levels of essential trace elements in a concentrated product* (powdered form) and allows the investigation of any discrepancies between declared and analyzed values; (2) *single intake* - the actual concentration of investigated essential trace elements consumed in one portion, (3) *daily dose* - depending on age and body weight.

3.1. Results of the dry weight (essential trace elements per kg of dried mass)

The results of the dry weight of analysed samples are given in Table 1.

The products are divided into groups related to the recommended age of product use. Results are given as a mean of each sample with standard deviation (SD) value. The determined essential trace elements were present in all of the samples. The concentration of Cu was in the range of 2.059–4.239 mg/kg, Mn concentration was in the range of 0.983–4.043 mg/kg and Zn concentration was in the range 29.098–61.169 mg/kg. The mean values of the essential trace elements divided into prescription FSMPs and MMPs available in Polish pharmacies are shown in Fig. 2.

The highest mean concentration was for Zn, and the lowest mean concentration was observed for Mn. Moreover, our results indicated that the prescription FSMPs contain similar levels of the essential trace elements under investigation when compared to MMPs available in Polish pharmacies.

3.2. One-time administration of investigated prescription FSMPs and modified milk products

The calculated concentration in the amount of milk corresponds to one portion (appropriate number of spoons) dissolved in a precisely defined volume of water specified by the producer. The results of one-time administration of investigated prescription FSMPs and MMPs available in Polish pharmacies are given in Table 2, as mg/L of milk.

3.3. Daily dose due to age and body weight

Proper complementary feeding including appropriate levels of essential trace elements is crucial for newborns and infants for optimal

Table 1
Concentrations of investigated essential trace elements: Cu, Mn and Zn in analysed samples (mg/kg).

Sample			Concentration [mg/kg]					
			Cu		Mn		Zn	
No.	Type	Code	Mean	SD	Mean	SD	Mean	SD
1.	prescription FSMPs	A 1	3.542	0.207	4.043	0.497	36.539	2.955
2.		A 2	4.239	0.164	2.562	0.010	52.471	5.684
3.		B 1	3.293	0.211	1.055	0.120	35.451	1.535
4.		B 2	2.059	0.138	1.039	0.156	29.098	1.044
5.		C 1	2.317	0.160	0.983	0.087	33.366	0.723
6.		C 2	2.499	0.008	1.104	0.080	37.977	3.327
7.	MMPs avaiable in	D 1	3.560	0.183	1.791	0.021	45.222	0.203
8.	Polish pharmacies	D 2	2.747	0.197	1.515	0.056	47.765	2.953
9.		E 1	3.484	0.505	1.017	0.159	31.431	1.409
10.		E 2	2.816	0.573	0.951	0.032	32.857	1.752
11.		F 1	2.637	0.265	1.353	0.039	49.869	0.099
12.		F 2	2.891	1.159	0.985	0.326	61.169	2.459

Applied acronyms: FSMPs - food for special medical purposes; MMPs – modified milk products; SD – standard deviation.

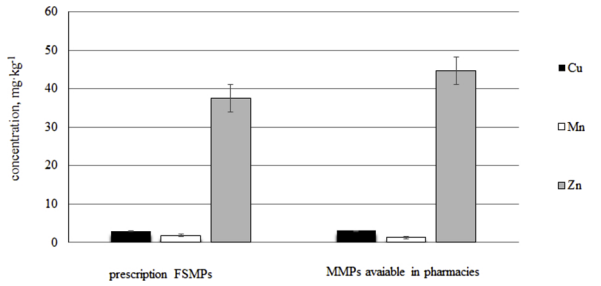

Fig. 2. The mean values of investigated essential trace elements divided in to prescription FSMPs and MMPs available in Polish pharmacies.

Table 2
Concentrations of investigated essential trace elements: Cu, Mn and Zn including one-time administration (mg/L of milk).

Sample			Cu concentration, mg/L	Mn concentration, mg/L	Zn concentration, mg/L
No.	Type	Code	Mean	Mean	Mean
1.	prescription	A 1	0.579	0.660	5.968
2.	FSMPs	A 2	0.692	0.418	8.570
3.		B 1	0.494	0.158	5.318
4.		B2	0.309	0.156	4.365
5.		C 1	0.348	0.147	5.005
6.		C 2	0.375	0.166	5.697
7.	MMPs	D 1	0.510	0.257	6.482
8.	avaiable in	D 2	0.394	0.217	6.846
9.	Polish	E 1	0.476	0.139	4.296
10.	pharmacies	E 2	0.385	0.130	4.490
11.		F 1	0.413	0.212	7.813
12.		F 2	0.453	0.154	9.583

Applied acronyms: FSMPs - food for special medical purposes; MMPs – modified milk products.

growth and development which is very individual and depends on many factors. However, all manufacturers place appropriate information on the packaging as a guide for the correct amounts of cool boiled water and milk in powder form to use. It is commonly known that the frequency of feeding depends on age (months) and body weight of the newborn or infant. Taking this into account the daily doses of the essential trace elements were calculated and presented in Table 3.

4. Discussion

4.1. Results of the dry weight (essential trace elements per kg of dried mass)

It should be noted that prescription FSMPs and MMPs available in Polish pharmacies contribute significantly to Cu, Mn and Zn levels in newborns and infants. Generally, each producer presents the declared quantitative composition of each essential trace element in a given product and it is possible to obtain information on the compliance of the results with the declared values. Analysed and declared values of all essential trace elements in the samples are presented in supported materials (see Table S6).

With respect to Cu, in most samples (8/12) declared values are higher than those determined in this study. There is no more than a 30% difference. However, most of the results indicate that the products do not meet the declared values and thus the product is not consistent with the description. Moreover, taking into account absorption – there exists a probability of deficiency of this essential trace element during application of these products (especially when diet of babies is based only on prescription FSMPs or MMPs available in Polish pharmacies. However, this probability should be considered minimal because there is no evidence of overt copper deficiency in the European population [6]. Of course, absence of Cu-deficiency across Europe in general does not mean that there are no local deficiencies, hence this aspect should be kept in mind.

Mn is very important from newborn's and infant's toxicological point of view [18–22], hence the appropriate level of this metal should be maintained. In all of the samples analysed the difference between the results obtained against the declared values are positive, hence in all samples levels of Mn are much higher than declared values. In three samples the Mn level is equal to or greater than twice the declared value (samples: C2, D2 and F2). It should also be noted that Mn levels in different types of milk products is very variable.

There is no doubt that Zn is one of the most important essential trace element for newborns and infants. It should be noted that of all the trace elements found in humans, only Fe is more abundant than Zn [12,23,24]. Moreover, this indicates that inadequate dietary intake of Zn due inappropriate diet (low zinc levels) can lead to a real risk of Zn deficiency [12]. In all samples there are slight differences between the declared composition and the declared values (the differences do not exceed 20% except sample F 2). In seven samples the declared values are higher than determined.

Additionally, our results provide valuable baseline data for other researchers for comparison of other kinds of prescription FSMPs and/or MMPs available in pharmacies.

4.2. One-time administration of applied prescription FSMPs and MMPs available in Polish pharmacies

The levels determined for these essential trace elements in the dry mass of the products are very important, especially for to safety and quality assessment. However, a more valuable measure for consumers is the actual amount of the essential trace elements in a single portion of final milk, as fed, because it can be valuable from the risk assessment point of view.

The EU has so far set thresholds for intake levels of the heavy metals (Pb, Cd and Hg) [25,26]. However, for many other metals (including Cu, Mn, Zn) levels that lead to deficiencies and chronic or acute poisonings are known, but no explicit thresholds have yet been set. Hence, it is not possible to discuss our results in the context of risk assessment. However, our results can be valuable for other researchers and are necessary for further considerations.

4.3. The daily dose

In the EU the scientific opinions on dietary reference values for Cu, Mn and Zn are published by European Food Safety Authority (EFSA). Below we discuss the results for the daily dose for each essential trace element separately.

Due to the absence of appropriate biomarkers of Cu status and the limitations of available balance studies, the EFSA was unable to derive Average Requirements (ARs) and Population Reference Intakes (PRIs) for Cu. Hence, Adequate Intake (AIs) was derived based on mean observed intakes in several countries in the EU, given that there is no evidence of overt Cu deficiency in the European population [6]. For infants aged 7–11 months (based on results from four surveys in infants), an AI of 0.4 mg/day was established. The EFSA applied extrapolation by allometric scaling of estimated Cu intake in exclusively breastfed infants aged 0–6 months results in an estimated intake at 7–11 months of 0.36 mg/day, which supports the AI of 0.4 mg/day. It should be emphasized that AIs should not be interpreted as upper limit for the intake of the trace elements but as a target value. In comparison to our results, only results for infancy at 6–12 months (subsequent milk formulas marked as "2") can be compared after calculations excluding mass of infants which consequently gives the following values: A2 – 0.415 mg/day; B2 – 0.185 mg/day; C2 – 0.225 mg/day; D2 – 0.236 mg/day; E2 – 0.231 mg/day; and F2 – 0.272 mg/day. Only sample A2 is characterised by a similar value to AI (0.4 mg/day). In other products, the Cu level is approximately a half level of AI. It should be noted that

Table 3
A daily dose of Cu, Mn and Zn in analysed samples (mg/kg bw/day).

	age	approximate body weight [kg]	samples																	
			prescription FSMPs									MMPs available in Polish pharmacies								
			A			B			C			D			E			F		
results for Cu	0 – 2 weeks	< 3.0 – 3.5	1	0.116	0.099	1	0.099	0.085	1	0.070	0.060	1	0.102	0.087	1	0.095	0.082	1	0.083	0.071
	2 – 4 weeks	3.5 – 4.0		0.099	0.087		0.085	0.074		0.060	0.052		0.087	0.077		0.082	0.071		0.071	0.062
	4 – 8 weeks	4.0 – 5.0		0.087	0.069		0.074	0.059		0.052	0.042		0.077	0.061		0.071	0.057		0.062	0.050
	8 – 16 weeks	5.0 – 6.5		0.069	0.053		0.059	0.046		0.042	0.032		0.061	0.047		0.057	0.044		0.050	0.038
	4 – 6 months	> 6.5		0.053			0.046			0.032			0.047			0.044			0.038	
	7 – 12 months	> 6.5	2	0.064			0.029		2	0.035		2	0.036		2	0.036		2	0.042	
results for Mn	age	approximate body weight [kg]	samples																	
			prescription FSMPs									MMPs available in Polish pharmacies								
			A			B			C			D			E			F		
	0 – 2 weeks	< 3.0 – 3.5	1	0.132	0.113	1	0.032	0.027	1	0.029	0.025	1	0.051	0.044	1	0.028	0.024	1	0.042	0.036
	2 – 4 weeks	3.5 – 4.0		0.113	0.099		0.027	0.024		0.025	0.022		0.044	0.039		0.024	0.021		0.036	0.032
	4 – 8 weeks	4.0 – 5.0		0.099	0.079		0.024	0.019		0.022	0.018		0.039	0.031		0.021	0.017		0.032	0.025
	8 – 16 weeks	5.0 – 6.5		0.079	0.061		0.019	0.015		0.018	0.014		0.031	0.024		0.017	0.013		0.025	0.020
	4 – 6 months	> 6.5		0.061			0.015			0.014			0.024			0.013			0.020	
	7 – 12 months	> 6.5	2	0.039			0.014		2	0.015		2	0.020		2	0.012		2	0.014	
results for Zn	age	approximate body weight [kg]	samples																	
			prescription FSMPs									MMPs available in Polish pharmacies								
			A			B			C			D			E			F		
	0 – 2 weeks	< 3.0 – 3.5	1	1.194	1.023	1	1.064	0.912	1	1.001	0.858	1	1.296	1.111	1	0.859	0.736	1	1.563	1.339
	2 – 4 weeks	3.5 – 4.0		1.023	0.895		0.912	0.798		0.858	0.751		1.111	0.972		0.736	0.644		1.339	1.172
	4 – 8 weeks	4.0 – 5.0		0.895	0.716		0.798	0.638		0.751	0.601		0.972	0.778		0.644	0.516		1.172	0.938
	8 – 16 weeks	5.0 – 6.5		0.716	0.551		0.638	0.491		0.601	0.462		0.778	0.598		0.516	0.397		0.938	0.721
	4 – 6 months	> 6.5		0.551			0.491			0.462			0.598			0.397			0.721	
	7 – 12 months	> 6.5	2	0.791			0.403		2	0.526		2	0.632		2	0.414		2	0.885	

Applied acronyms and description of numbers: bw – body weight. FSMPs - food for special medical purposes; MMPs – modified milk products; 1 – initial milk formulas (0–6 months); 2 – subsequent milk formulas (6–12 months).

these products represent the only source of the Cu, hence most products analysed do not contain enough Cu to achieve the recommended level of intake. Conversely, none of the investigated samples represents a health hazard to the consumer due to excess but there is a potential risk associated with deficiency of Cu in the diet.

The estimated AI of Mn by EFSA is based on observed intakes of this essential trace element together with the absence of evidence of signs of deficiency. The respective AIs was established as 0.5 mg/day in infants aged 7–11 months [10]. Hence, in analogy to Cu, only results for infancy at 6–12 months (subsequent milk formulas marked as "2") can be compared after calculations excluding mass of infants which consequently gives the following values: A2 – 0.251 mg/day; B2 – 0.094 mg/day; C2 – 0.100 mg/day; D2 – 0.130 mg/day; E2 – 0.078 mg/day; and F2 – 0.092 mg/day. In all products, the Mn level is below of AI (0,5 mg/day). It should be noted that AI does not mean a requirement of nutrients - it is the median or average value of the intake of the population without deficiency. According to our findings, none of the investigated samples represents a health hazard to the consumer due to excess of Mn in the diet. Taking into account also fact that Mn requirement value and the symptoms of Mn deficiency are unknown it is not possible to made any expressions about the required amount of this element in the diet of babies.

Concerning Zn, the Institute of Medicine (IOM) set an Adequate Intake (AI) of 2.0 mg/day for infants aged 0–6 months [27]. Additionally, the estimated physiological zinc requirement for infants aged 7–11 months is 0.732 mg/day [27]. The obtained results can be compared after calculations excluding mass of infants in two age groups:

- 0–6 months: A2 – 3.581 mg/day; B2 – 3.191 mg/day; C2 – 3.003 mg/day; D2 – 3.889 mg/day; E2 – 2.578 mg/day; and F2 – 4.688 mg/day;
- 7 – 11 months: A2 – 5.142 mg/day; B2 – 2.619 mg/day; C2 – 3.418 mg/day; D2 – 4.108 mg/day; E2 – 2.694 mg/day; and F2 – 5.750 mg/day.

The results obtained for the first age group (0–6 months) exceed the value of AI (especially D2 and F2). On the other hand, the results for second age group (7–11 months) are much higher than the estimated physiological zinc requirement. However, most of the results indicate that the products do not meet the declared values, and thus the product is not consistent with the description. Taking into account fact that Zn does not accumulate in the body [12], the excess of Zn in the products analyzed is not a serious threat. Accordingly, none of the analysed products represent a health hazard for the newborns and infants due to excess and deficiency.

5. Conclusions

For proper complementary feeding of babies in infancy period, the appropriate level of essential trace elements in prescription FSMPs or MMPs available in pharmacies is required. There is currently a dearth of published literature, in terms of toxicological aspects, around the essential trace elements Cu, Mn and Zn and in safety, risk and quality assessment of pharmaceutical products.

Taking into account our raw results, there are slight differences between the declared composition and the declared values in all cases – in most samples (8/12) declared values are higher than determined. However, it can be also concluded that the prescription FSMPs in comparison to MMPs available in Polish pharmacies contain similar amounts of investigated essential trace elements.

The results of one-time administration show that none of the analysed products represent a health hazard for the newborns and infants due to excess of Cu, Mn and Zn levels. It should be noted that the Cu levels (except sample A2) and Mn levels are all below of AI.

Daily dose calculations (mg/kg bw/day) confirm that none of the products represent a health hazard due to excess of elements for babies in the infancy period.

It can be concluded that our study confirms that a diet based on prescription FSMPs and MMPs available in Polish pharmacies, alone, does not fulfill, in most cases, the infant's dietary need for Cu and Mn.

All the analysed prescription FSMPs and MMPs do not represent a health hazard to the newborns and infants in relation to excess Cu, Mn and Zn levels. Moreover, our results could be valuable to other researchers to compare the results for other kind of prescription FSMPs and/or MMPs available in pharmacies from other countries. A broader study considering prescription FSMPs and MMPs available in pharmacies from other countries, would be valuable like previously described [28,29].

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jtemb.2019.03.001.

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