



# The Toxicological Analysis of Ni and Cr in Prescription Food for Special Medical Purposes and Modified Milk Products for Babies in Infancy Available in Pharmacies in Poland

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## Abstract

Prescription food for special medical purposes (FSMPs) and modified milk products (MMPs) for babies in the infancy period available in pharmacies are increasingly frequently used for newborns and infants—especially in cases where allergies and food-borne diseases are diagnosed. However, there is a lack of scientific study around the safety assessment of the elemental impurities in these products. Importantly, the allergen Ni and the problematic metal Cr are little considered. Hence, the aim of this article was the toxicological analysis of Ni and Cr impurities in prescription FSMPs ( $n=6$ ) and MMPs ( $n=6$ ) for newborns and infants available in Polish pharmacies. For the best safety assessment, we include three approaches including (1) the levels of Ni and Cr in powdered products, (2) assessment of the daily dose depending on age and body weight of newborns and infants, and (3) the weekly intake of Ni and Cr in samples in comparison to provisional tolerable weekly intake (PTWI). Our results show that, on the basis of our data, the products from pharmacies in Poland investigated in this study do not represent a real health hazard to newborns and infants, although there may be a requirement for the monitoring of levels of Ni. Our results are pioneer and provide valuable data for other scientists and manufacturers.

**Keywords** Elemental impurities · Safety assessment · Nickel · Chromium · Prescription food for special medical purposes · Modified milk products for babies · Infants

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## Abbreviations

|       |                                     |
|-------|-------------------------------------|
| AAS   | Atomic absorption spectrometry      |
| AI    | Adequate intake                     |
| bw    | Body weight                         |
| FSMPs | Food for special medical purposes   |
| MMPs  | Modified milk products              |
| PTWI  | Provisional tolerable weekly intake |
| SD    | Standard deviation                  |
| TDI   | Tolerable daily intake              |
| WHO   | World Health Organization           |

## Introduction

Based on WHO data (2009) [1], in developing countries, less than 40% of newborns are exclusively breastfed. However, in European Union countries, only 3% of infants are exclusively breastfed at this age [2]. Based on the report on breastfeeding status in Poland 2013 [3], 98% of mothers begin to breastfeed

newborns; however, the numbers of breastfeeding mothers drop significantly to 46% in the first month after childbirth. Hence, milk-based formulas, modified milk products (MMPs), food for special medical purposes (FSMPs), and milk substitutes are generally recommended and widely used in developed countries. These products, dedicated to babies in the infancy period, serve as substitutes for human milk; hence, they play a crucial role in infant nutrition. It should be emphasized that in the absence of breast milk, these types of products are the only source of essential trace elements (especially Cu, Mn, Zn) [4] but also act as sources of toxic metals (including Pb, Cd, Hg, As) and allergenic metals (e.g., Ni, Cr, Co). While in the contemporary scientific literature there are articles focused on the determination of essential trace elements [5–7] and toxic elements [8–10] in commercially available infant formulas, there is a lack of information about allergic metals like Ni and problematic elements like Cr in prescription FSMPs and MMPs available in pharmacies.

The problem of Ni as an impurity in prescription FSMPs and MMPs available in pharmacies is very important. It should be emphasized that Ni seems to be an essential micronutrient in animals, and perhaps could be essential for humans [11]; however, its precise function in humans is still unknown. What is more, in the literature, there is contradictory information that this element is nutritionally not essential for humans [12]. It is well known that humans generally become sensitized to Ni after prolonged contact of Ni with the skin [13]. It is also known that a single dose via an oral route can also be important because Ni administered in drinking water and powdered milk-based products can induce dermatitis in sensitized individuals [13]. This is especially important with respect to feeding by prescription FSMPs and MMPs available in pharmacies because the milk is made by dissolving a powdered product in drinking water.

Similarly, Cr is a very problematic element but is underestimated in the infant's toxicology because there is a lack of studies dedicated to this element. It should be underlined that Cr is no longer considered an essential element for animals and humans [14]. It is acknowledged that a variety of oxidation states of Cr are known, but the most important are Cr(II), Cr(III), and also Cr(VI). Cr(II) is easily oxidized and is applied as a reducing agent in chemical synthesis [15]. Cr(III) is the most abundant form in the environment, and is an essential element that plays a role in glucose metabolism. Cr(III) deficiency causes changes in the metabolism of glucose and lipids. What is more, this Cr(III) may be related with maturity to cardiovascular diseases, onset diabetes, and also nervous system disorders [15]. Although insufficient Cr(III) intake was implied as a possible risk factor of the development of diabetes, its role is still not fully known. However, Cr(III) is still a very popular component of dietary supplements, recommended for diabetes patients [14]. In turn, compounds of Cr(VI) do not occur in nature due to the fact that they are synthesized. In the gastrointestinal tract, Cr(VI) is reduced to Cr(III). Hence, only intakes that exceed the reducing capacity of the stomach will result in significant absorption of

Cr(VI) across the gastrointestinal mucosa [16]. In most cases, Cr(II), Cr(III), and Cr(VI) residues are usually measured as total Cr. However, studies including Cr levels in milk-based products for infants are very rare, but if they are, they are not considered from a toxicological point of view.

In order to increase the knowledge around the exposure of newborns and infants to Ni and Cr, we have assessed the levels of these elements in prescription FSMPs and MMPs available in Polish pharmacies. Scientific studies including prescription FSMPs are very rare in the scientific literature because these pharmaceutical products are usually issued on a pharmacy prescription; hence, it is difficult to obtain these samples. On the other hand, there are many articles about the determination of trace elements in MMPs but all of them are commercially available in the local market, not in pharmacies. Additional justification for considering this kind of samples is the fact that, usually, there is a widespread belief that consumers are usually convinced that products available in pharmacies are better than those available in the market.

Hence, the aim of this study was the toxicological analysis of Ni and Cr impurities in prescription food for special medical purposes and modified milk products for babies in the infancy period available in pharmacies in Poland. In our study, we applied three approaches which are important from the toxicological point of view:

- the levels of Ni and Cr in powdered products;
- the daily dose depending on age and body weight of newborns and infants
- the weekly intake of Ni and Cr in samples in comparison to provisional tolerable weekly intake (PTWI).

## Materials and Methods

### Instrumentation

Ultrapure demineralized water had been obtained by Milli-Q water purification system (Millipore, Bedford, MA, USA). The samples were digested using a microwave digestion system (CEM, Matthews, NC, USA). A Perkin-Elmer 5100 ZL atomic absorption spectrometer (Perkin-Elmer, Norwalk, CT, USA) with Zeeman background correction and with electrothermal atomization (ETAAS technique) was used for determination of Ni and Cr using the appropriate hollow cathode lamps. All detailed information about instrumentation is described in Supplementary Materials 1.

### Reagents and Solutions

All chemicals and metal stock standard solutions were obtained from Merck (Darmstadt, Germany) and were

prepared using ultrapure demineralized water. The purge gas was argon at purity 99.99%. The certified reference material (INCT-CF-3) was purchased from the Institute of Nuclear Chemistry and Technology, Department of Analytical Chemistry (Warsaw, Poland).

## Description of Study Area

All steps of the study area are summarized in the graphical workflow—Fig. 1.

The samples ( $n = 12$ ) were six prescription FSMPs (A–C) and six MMPs (D–F) available only in pharmacies. The samples were initial milk formulas (numbered as “1”; 0–6 months) and subsequent milk formulas from the same manufacturer (numbered as “2”; 7–12 months). The coding system of investigated samples was as follows: letters (A–F) mean the manufacturer, and the numbers (1 or 2) indicate milk type (initial (1)/subsequent (2)). All pharmaceutical products were obtained from pharmacies in Poland (Kraków or Niepołomice). The samples represent all available prescription FSMPs and MMPs available in Polish pharmacies.

Prior to the measurements, samples were dried in an oven at 70 °C in a weighed ceramic crucible for 48 h to constant weight. The moisture content was calculated to be about 2.5%. Ni and Cr determination in digested samples was done using electrothermal atomization. Pyrolytically coated graphite tubes with L’vovs platforms were used. Calibration curves were plotted with standard solutions of Ni and Cr (12.5–100 µg/L).

Data processing and all basic descriptive calculations were performed using Excel 2010 (Microsoft Office). The resultant data of three independent replicates were expressed as the mean  $\pm$  standard deviation. All detailed information about the analytical methodology (calibration strategy and quality control) is described in Supplementary Materials 2.

## Results and Discussion

### The Level of Ni and Cr in Powdered Prescription FSMPs and MMPs Available in Polish Pharmacies

The “raw” results for the samples are given in Supplementary Materials 3, as microgram metal per kilogram of dried mass. Profiles of Ni and Cr impurities in prescription FSMPs and MMPs available in pharmacies in Poland are given in Fig. 2.

The presence of Ni in all samples has been observed in the range 50.49–383.49 µg/kg. The highest level of Ni was observed in FSMP A1 ( $383.46 \pm 16.54$  µg/kg). The lowest level of this element was in FSMP C1 ( $50.49 \pm 4.72$  µg/kg). The comparison of mean results for Ni shows that the mean  $\pm$  standard deviation (SD) of prescription of FSMP and MMPs available in pharmacies were found to be similar, i.e.,  $144.46 \pm 8.06$  µg/kg and  $157.66 \pm 12.40$  µg/kg, for FSMPs and MMPs respectively. As can be seen, the biggest differences are observed (50.49–383.46 µg/kg for FSMPs and 100.58–194.04 µg/kg for MMPs). Notwithstanding, considering all type of products,

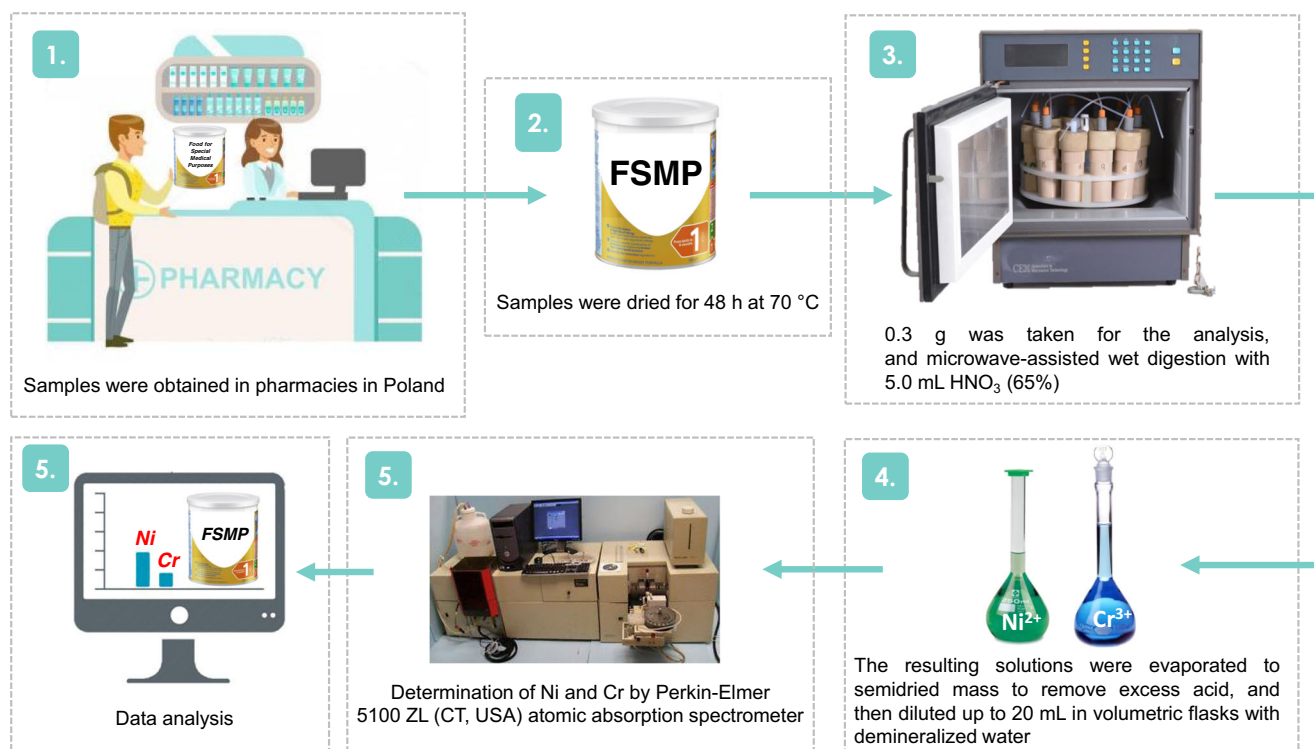
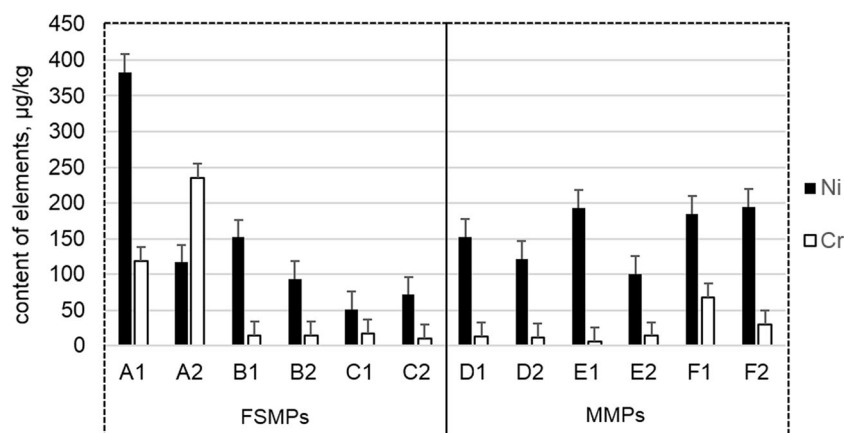


**Fig. 1** Steps in the toxicological analysis of Ni and Cr in prescription FSMPs and MMPs available in Polish pharmacies

**Fig. 2** Profile of Ni and Cr impurities in prescription FSMPs and MMPs available in Polish pharmacies



samples of initial milk formulas (0–6 months) in most cases (except two products, C and F) are characterized by higher levels of this element than the corresponding subsequent milk formulas (7–12 months); the ratios of levels of Ni in initial milk formulas to subsequent milk formulas are 3.28 for product A, 1.63 for product B, 1.26 for product D, and 1.92 for product E. It is difficult to compare our results to others because, to the best of our knowledge, there is a lack of appropriate and actual data (scientific articles, regulations, monographs, etc.) about levels of Ni especially in FSMPs in the public domain. Hence, the levels of Ni in the dry mass of the analyzed prescription FSMPs described provide pioneer data and may be of value to other researchers and manufacturers. Considering MMPs, few articles describe levels of Ni in this kind of product. However, it should be emphasized that samples are usually infant milk formulas from sources other than pharmacies—generally mostly available in local markets. For example, Arif et al. [17] found that Ni was completely absent in all investigated formula milk in Pakistan. Confirmation of this type of result is also found in Ikem et al. [18], where Ni was not detected in all investigated infant formula samples from the USA, the UK, and Nigeria. On the other hand, the concentration of this element in infant formula milk brands in Nairobi market (Kenya) was in the range 28–32 µg/kg—the low end of the range found in our study. From the regional point of view, very valuable results arise from the analysis of infant formulas available on Polish markets described by Chajduk et al. [19], where the mean concentration of Ni in cow-based milk formulas was in the range 70.9–80.2 µg/kg—the mid-range in our study.

As in the case of Ni, the presence of Cr in all samples has been also observed but with a very wide range in values, i.e., 6.44–234.77 µg/kg. The lowest level of Cr was observed in MMP E1 ( $6.44 \pm 1.23$  µg/kg), and the highest level of this element was observed in FSMP A2 ( $234.77 \pm 10.09$  µg/kg). Additionally, the biggest differences are observed especially for FSMPs (10.68–234.77 µg/kg); for MMPs, the differences also ranged over an order of magnitude (6.44–67.38 µg/kg). Comparison of Cr levels considering differences between initial milk formulas (0–6) with subsequent milk formulas (7–

12 months) shows that there are few differences. The comparison of the results for FSMPs with scientific data is not possible because there is a lack of appropriate scientific data for this kind of product in the public domain. Hence, to the best of our knowledge, the levels of Cr in the prescription FSMPs described provide the first such publicly available data and may be of value to other researchers and/or manufacturers especially due to the nutritional importance of this biological trace element. There are a limited number of papers about levels of Cr in infant milk formulas which are valuable for comparison to our results for MMPs available in Polish pharmacies. Melø et al. [20] show that in two commercially available infant formula from the Norwegian market, the mean level of Cr was 0.2 µg/kg. On the other hand, the results for Cr levels in infant formulas available on Polish markets described by Chajduk et al. [19] show that the mean concentration of this element in cow-based milk formulas was below 100 µg/kg. These results confirm the reliability of our results for MMPs (range 6.44–67.38 µg/kg).

### Safety Assessment of Ni and Cr in Analyzed Samples Related to PTWI

It should be emphasized that while information about results of Ni and Cr levels in the samples in this study (in the dry mass) may be crucial, for example, to other investigators for comparison purposes, the most valuable information for risk assessment is the daily and weekly intake of Ni and Cr in the samples related to appropriate limits. However, to calculate the daily and weekly intake of analyzed metals in the investigated samples, the actual amount of these metals in the single portion of milk once constituted was calculated, i.e., the concentration of metals in the one-time administration of investigated FSMPs and MMPs. For better readability, the results of Ni and Cr considering the one-time administration are given in Supplementary Materials 4. The second step was the calculation of daily dose, depending on age and body weight. It should be noted that the diet for newborns or infants is very individual and based usually on information from the

**Table 1** The weekly intake of Ni in analyzed samples ( $\mu\text{g/kg bw/week}$ )

| 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 87.685–75.158    | 1 31.849–27.299 | 1 10.602–9.087 | 1 30.598–26.227                     | 1 36.974–31.692 | 1 40.411–34.638 |
| 2–4 weeks   | 3.5–4.0                      | 81.422–85.493      | 27.299–23.886   | 9.845–10.337   | 28.413–29.833                       | 34.333–36.050   | 37.525–39.401   |
| 4–8 weeks   | 4.0–5.0                      | 93.165–74.532      | 23.886–19.109   | 11.265–9.012   | 32.511–26.009                       | 39.285–31.428   | 42.937–34.349   |
| 8–16 weeks  | 5.0–6.5                      | 70.148–67.450      | 19.109–14.699   | 8.482–8.155    | 24.479–23.537                       | 29.579–28.442   | 32.329–31.085   |
| 4–6 months  | > 6.5                        | 62.054             | 14.699          | 7.503          | 21.654                              | 26.166          | 28.599          |
| 6–12 months | > 6.5                        | 2 11.789           | 2 9.021         | 2 6.644        | 2 1.539                             | 2 8.512         | 2 18.824        |

*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)

packaging as a guide for the standardized amounts of cool boiled water and milk (powder form) to apply. The proportions depend on manufacturers but usually are very similar. The frequency of feeding depends on the age (months) and the body weight of the newborns or infants. Hence, the daily and weekly doses were calculated based on information from manufacturers (information on the packaging) for each product. The results of a daily dose of Ni and Cr in analyzed samples ( $\mu\text{g/kg bw/day}$ ) are given in Supplementary Materials 5. Based on our results, the weekly intake of Ni and Cr in the samples ( $\mu\text{g/kg bw/week}$ ) is shown in Table 1 and Table 2 respectively.

Considering daily dietary exposure, the data obtained for Ni was in the range 0.949–13.309  $\mu\text{g/kg bw/day}$  for prescription FSMPs and in the range 1.216–6.134  $\mu\text{g/kg bw/day}$  for MMPs (see Supplementary Materials 5). All results are well below the WHO TDI for Ni (11  $\mu\text{g/kg bw/day}$ ) except initial milk formula A1 where the level was slightly above this value (11.637–13.309  $\mu\text{g/kg bw/day}$ ). According to PTWI, the JECFA has established a PTWI for Ni of 35  $\mu\text{g/kg bw/week}$  [21–23]. Most results are

below the established PTWI, except product A (approximately twice higher level) and F (similar results to PTWI). Hence, most of the investigated samples do not represent a health hazard to infants. It may be, however, that there is a greater need for a statutory monitoring requirement for Ni in these products.

Considering Cr, it should be noted that Directive 2006/141/EC, on infant and follow-on formula, does not set minimum and maximum levels for Cr [24]. Hence, for infants aged 7–12 months, the IOM [25] in 2001 set an AI as 5.5  $\mu\text{g/kg bw/day}$  based on Cr intake from human milk and complementary foods. Considering daily dietary exposure, the data obtained for Cr in subsequent milk formulas was in the range 0.142–3.392  $\mu\text{g/kg bw/day}$  for prescription FSMPs and in the range 0.155–0.411  $\mu\text{g/kg bw/day}$  for MMPs (see Supplementary Materials 5). Hence, our results are well below the established AI. On the other hand, the PTWI for Cr set by WHO/FAO is 23.3 mg/kg bw/week (23,300  $\mu\text{g/kg bw/week}$ ) [24]. Our results are greatly below the established PTWI value. All of the investigated samples do not represent a health hazard to infants due to Cr levels.

**Table 2** The weekly intake of Cr in analyzed samples ( $\mu\text{g/kg bw/week}$ )

| 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 27.220–23.332    | 1 2.985–2.558 | 1 3.490–2.992 | 1 2.635–2.258                       | 1 1.232–1.056 | 1 14.778–12.667 |
| 2–4 weeks   | 3.5–4.0                      | 25.276–26.540      | 2.558–2.239   | 3.241–3.403   | 2.447–2.569                         | 1.144–1.201   | 13.723–14.409   |
| 4–8 weeks   | 4.0–5.0                      | 28.921–23.137      | 2.239–1.791   | 3.708–2.967   | 2.799–2.240                         | 1.309–1.047   | 15.702–12.562   |
| 8–16 weeks  | 5.0–6.5                      | 21.776–20.939      | 1.791–1.378   | 3.482–2.685   | 2.108–2.027                         | 0.986–0.948   | 11.823–11.368   |
| 4–6 months  | > 6.5                        | 19.264             | 1.378         | 2.470         | 1.865                               | 0.872         | 10.459          |
| 6–12 months | > 6.5                        | 2 23.745           | 2 1.818       | 2 0.992       | 2 1.085                             | 2 1.165       | 2 2.880         |

*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)

## Conclusions and Recommendations

Our results for Ni and Cr levels show that prescription FSMPs and modified milk products contribute significantly to this element exposure of newborns and infants. It should be noted that it is difficult to compare our “raw” results with other scientific data because to the best of our knowledge, there is a lack of appropriate sources about levels of investigated elements in prescription FSMPs and MMPs available in pharmacies in the public domain. However, studies about the levels of Ni and Cr in commercially available milk-based products for newborns and infants confirm the reliability of our results.

Considering daily intake of Ni, our results are well below the WHO TDI for Ni (11 µg/kg bw/day) except initial milk formula A1 (11.637–13.309 µg/kg bw/day). Weekly intake of Ni in most samples does not exceed the PTWI (35 µg/kg bw/week) (except product A and F). However, it should be remembered that the absorption of Ni from the analyzed samples may be significantly lower than prediction which may make these products safe for consumers. However, it may be necessary to implement a monitoring policy around Ni levels. On the other hand, our results for Cr level are well below in all samples in comparison to the AI (5.5 µg/kg bw/day) and all results are greatly below the established PTWI value (23.3 mg/kg bw/week).

Our results show that all analyzed products including prescription FSMPs and MMPs available in pharmacies in Poland should not represent a serious health hazard to the newborns and infants due to Ni and Cr levels.

Since our results around Ni and Cr levels provide pioneer data, they may be valuable for other investigators and manufacturers. Due to the fact that these kinds of studies are very rare, it would be valuable to carry out a broader range of study considering more elements and products from pharmacies in different countries in the European Union.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed Consent** Informed consent is not applicable in this study.

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