

NICKEL RISK ASSESSMENT THROUGH THE CONSUMPTION OF FLOUR-BASED PRODUCTS AND CEREALS

SEDA STEPANYAN

Center for Ecological-Noosphere Studies National Academy of Sciences, RA
Junior Scientific researcher
seda.stepanyan@cens.am

MONIKA KHACHATRYAN

Center for Ecological-Noosphere Studies National Academy of Sciences, RA
Expert
monika.khachatryan@cens.am

DAVIT PIPOYAN

Center for Ecological-Noosphere Studies National Academy of Sciences, RA
Head of the “Informational - analytical center for risk assessment of food chain”
Doctor of Food Science (Italy)
david.pipoyan@cens.am

DOI: 10.54503/2579-2903-2022.1-190

Abstract

Flour-based products and cereals are one of the most consumed food items in Armenia. The aim of this study is to conduct Ni risk assessment through the consumption of flour-based products and cereals. The consumption data of flour-based products and cereals has been gathered through a 24-hour recall survey, including 1400 adult respondents of the Republic of Armenia. Ni risk assessment has been conducted through a Margin of Exposure (MOE) approach. Ni contents were analyzed using atomic absorption spectrometry. The Estimated Daily Intake (EDI) values ranged from $8.63\text{E-}06$ to $5.55\text{E-}04$ mg/kg bw per day and did not exceed the threshold. The average EDI was equal to $1.53\text{E-}04$ mg/kg bw per day. In all the regions, MOE values were lower than 30 in case of the intake of bread, lavash, buckwheat, emmer and groat. In case of pasta intake, the MOEs were lower than 30 only in Armavir and Lori regions, while in other regions MOEs were slightly above 30. Only for rice, the MOE values were higher than 30, indicating no possible health risks. Overall, the intake of products with MOEs lower than 30 may cause health problems and allergies, especially for Ni sensitized individuals.

Keywords and phrases: nickel, flour-based products, cereals, risk, estimated daily intake, margin of exposure.

**ՆԻԿԵԼԻ ՌԻՍԿԻ ԳՆԱՀԱՏՈՒՄԸ ԱԼՐԱՅԻՆ ՀԵՆՔՈՎ ՄԹԵՐՔՆԵՐԻ ԵՎ
ՀԱՏԻԿԵՂԵՆԻ ՍՊԱՌՄԱՆ ԴԵՊՔՈՒՄ**

ՍԵՂԱ ՍՏԵՓԱՆՅԱՆ

ՀՀ Գիտությունների ազգային ակադեմիայի
էկոլոգանոոսֆերային հետազոտությունների կենտրոնի
կրտսեր գիտաշխատող
seda.stepanyan@cens.am

ՄՈՆԻԿԱ ԽԱՉԱՏՐՅԱՆ

ՀՀ Գիտությունների ազգային ակադեմիայի
էկոլոգանոոսֆերային հետազոտությունների կենտրոնի
փորձագետ
monika.khachatryan@cens.am

ԴԱՎԻԹ ՊԻՊՈՅԱՆ

ՀՀ Գիտությունների ազգային ակադեմիայի
էկոլոգանոոսֆերային հետազոտությունների կենտրոնի
սննդի շղթայի ռիսկերի գնահատման տեղեկատվական վերլուծական
կենտրոնի ղեկավար,
սննդագիտության դոկտոր (Իտալիա)
david.pipoyan@cens.am

Համառոտագիր

Այս ուսումնասիրության նպատակն է արլային հենքով մթերքների և հացահատիկների սպառման միջոցով գնահատել նիկելի ազդեցությունը, քանի որ այդ մթերքները լայն սպառում ունեն Հայաստանում: Արլային հենքով մթերքների և հատիկեղենի սպառումն ուսումնասիրելու համար օգտագործվել է 24-ժամյա հետկանչի մեթոդը Հայաստանի չափահաս բնակչության շրջանում (1400 հարցվող): Ռիսկի գնահատումը կատարվել է ներազդեցության սահմանի մեթոդով: Նիկելի պարունակությունները նմուշներում որոշվել են ատոմային աբսորբցիոն սպեկտրոմետրով: Հաշվարկվել են նիկելի գնահատված ամենօրյա ընդունման արժեքները, որոնք չեն գերազանցել թույլատրելի շեմը: Արժեքները տատանվում են $8.63E-06$ -ից $5.55E-04$ մգ/կգ մ.գ./օր-ի սահմաններում: Միջին արժեքը կազմում է $1.53E-04$ մգ/կգ մ.գ./օր: Բոլոր մարզերում հացի, լավաշի, հնդկաձավարի, հաճարի և ձավարի դեպքում ներազդեցության սահմանի 30-ից ցածր արժեքներ են ստացվել: Արմավիրի և Լոռու մարզերում մակարոնեղենի սպառման դեպքում ներազդեցության սահմանի ցուցանիշները ցածր են եղել 30-ից, իսկ մնացած մարզերում ցուցանիշները փոքր-

ինչ գերազանցել են 30-ը: Բրնձի սպառումը չի գնահատվում ռիսկային, քանի որ ստացվել են ներազդեցության սահմանի 30-ից բարձր արժեքներ: Ներազդեցության սահմանի 30-ից ցածր արժեքներ ունեցող մթերքների սպառումը տվյալ մարզերում կարող է առաջացնել առողջական խնդիրներ, ալերգիաներ նիկելի նկատմամբ զգայուն և ալերգիկ մարդկանց մոտ:

Բանալի բառեր և բառակապակցություններ. նիկել, ալրային հենքով մթերքներ, հատիկեղեն, ռիսկ, գնահատված ամենօրյա ընդունում, ներազդեցության սահման:

ОЦЕНКА РИСКА НИКЕЛЯ ПРИ ПОТРЕБЛЕНИИ МУЧНОЙ ПРОДУКЦИИ И ЗЛАКОВ

СЕДА СТЕПАНЯН

Центр эколого-ноосферных исследований НАН РА
младший научный сотрудник
seda.stepanyan@cens.am

МОНИКА ХАЧАТРЯН

Центр эколого-ноосферных исследований НАН РА
Эксперт
monika.khachatryan@cens.am

ДАВИД ПИПОЯН

Центр эколого-ноосферных исследований НАН РА
руководитель «Информационно-аналитического центра по оценке рисков
пищевой цепи»
доктор пищевых наук (Италия)
david.pipoyan@cens.am

Аннотация

Мучные изделия и злаки являются одними из наиболее часто потребляемых продуктов питания в Армении. Целью данного исследования является проведение оценки риска никеля при потреблении продуктов на основе муки и злаков. Данные о потреблении продуктов на основе муки и злаков были собраны в ходе 24-часового опроса, в котором приняли участие 1400 взрослых респондентов Республики Армения. Оценка риска Ni была проведена с использованием подхода допустимого уровня воздействия (МОЕ). Содержание никеля анализировали с помощью атомно-абсорбционной спектрометрии. Расчетное суточное потребление (EDI) колебалось от $8,63E-06$ до $5,55E-04$ мг/кг массы тела в день и не превышало порогового значения. Средний EDI был равен $1,53E-04$ мг/кг массы тела в сутки. Во всех регионах значения МОЕ были ниже 30 при потреблении хлеба, лаваша, гречки, полбы и крупы. В случае потребления макаронных изделий МОЕ были ниже 30 только в Армавирской и Лорийской областях, в то время как в других регионах МОЕ были немного выше 30. Только для риса значения МОЕ были выше 30, что указывает на отсутствие возможных рисков для здоровья. В целом потребление продуктов с МОЕ ниже 30 может вызвать проблемы со здоровьем и аллергию, особенно у людей, чувствительных к никелю.

Ключевые слова и словосочетания: никель, продукты на основе муки, злаки, риск, предполагаемая суточная доза, допустимый уровень воздействия

Introduction

Nickel (Ni) is a hard, silvery-white transition metal. It exists in several oxidative states; however, Ni^{2+} is the most prevalent in the environment and biological systems [4]. Naturally, Ni occurs in the Earth's crust, combined with oxygen and sulfur. Ni may

also be emitted from volcanoes and occur in the soil, alone or in combination with other elements [6, 11].

Ni may end up in foods by being absorbed from the soil into the plant through roots [16]. Due to its physical and chemical properties, Ni is used as a catalyst in the chemical and food industry [5]. Therefore, Ni may also be released from food contact materials, including packaging material, cooking utensils and storage containers [4].

Human exposure to Ni may occur through inhalation, ingestion, or dermal contact. One of the most common ways of dermal exposure to Ni can occur via coins [9]. However, for humans, ingestion through water and food is the most concerning since Ni may be a contaminant in drinking water or food [5]. High concentrations of Ni have been found in wild mushrooms, cocoa and cocoa products, beans, seeds, nuts, and grains [4].

There is evidence that Ni is an essential nutrient for some microorganisms, plants, and animal species, but its nutritional value for humans has not been established [5]. Ni compounds are carcinogenic to humans (Group 1), Ni metal is classified as possibly carcinogenic to humans (Group 2B) [6]. Besides, Ni can also act as an immunotoxic, embryotoxic, teratogenic, and allergenic agent [15]. Depending on the dose and length of exposure, Ni can have both acute and chronic health effects, including contact dermatitis, cardiovascular disease, asthma, lung fibrosis, and respiratory tract cancer [10].

Several investigations have been conducted in Armenia showing that Ni can have various health risks, including carcinogenic risk. Particularly, in the regions of Syunik and Shirak, carcinogenic risk of Ni has been identified via consumption of honey, while in the Alaverdi region, the Estimated Daily Intake (EDI) of Ni exceeded the Tolerable Daily Intake (TDI) in case of fruit and vegetable consumption [12, 14]. Besides these food products, concerns for consumer safety were identified in the case of dietary exposure to Ni via consumption of flour-based products. In particular, the estimated mean Ni intake made 36.2% of the TDI among the population of Yerevan, Armenia. According to the obtained data Margin of Exposure (MOE) lower than 10 were observed for Ni in all white bread Clusters, in two Clusters (N2 and N3) of lavash and cookies one Cluster (N3) [13].

Flour-based products and cereals substantially contribute to the diet of Armenians [13]. According to the Statistical Committee of the Republic of Armenia, the average daily intake of bread and bread products in the country is estimated at 461.1 g per capita [17]. Taking into consideration the importance of flour-based products and cereals in the Armenian diet, as well as the absence of prior investigation on Ni risk assessment in the whole country, this study aims to assess the exposure to Ni and the related human health risks, via consumption of the main flour-based products and cereals (white bread, lavash, pasta, and waffles and cookies, rice, buckwheat, emmer, groat) among the adult Armenian population. The work has been carried out in the frame of “20TTCG-4A001, Strengthening Scientific and Methodological Capacity for Assessing Food Security and Nutrients” program.

Material and Methods

Food selection, sampling, and analysis

The selection of flour-based products and cereals was based on the frequency and consumption amount (daily consumption of more than 1 gram was considered) of each product. The most widely consumed products were ‘Bread’, ‘Lavash’, ‘Pasta’

(including macaroni, vermicelli, spaghetti), ‘Waffles and cookies’, ‘Rice’, ‘Buckwheat’, ‘Emmer and groat’. Overall, the list consisted of 10 core food products. Each food corresponded to a pooled sample composed of 8 different foods, selected according to market share, processing, and origin. Sampling was performed between November 2018 and July 2019. The food items were bought at supermarkets, markets, and food vendors, selected to cover all the major retailers in Armenia. Ni contents were analyzed using atomic absorption spectrometry. Sampling procedures were done based on the Total Diet Study (TDS) Methodology and on the standard operational procedures (SOPs) developed by the staff of the Center for Ecological-Noosphere Studies NAS RA (CENS) [13, 3, 7].

Consumption data and analysis

The 24-h recall method was used to obtain data for flour-based food and cereals consumption by Armenia’s adult population (18–80 years old and above). The data collection period was from February to September 2021. The information was collected via face-to-face and telephone interviews, using pre-designed forms.

Overall, 1400 residents of Armenia were interviewed. This survey included all the regions of Armenia: Armavir, Ararat, Aragatsotn, Gegharkunik, Kotayk, Lori, Shirak, Syunik, Tavush, Vayots Dzor, and Yerevan. To obtain more accurate and representative data, survey participants were chosen from 12 administrative districts of Yerevan, with equal access.

SPSS software (IBM SPSS, v.22) was used for data entry and statistical analysis.

Exposure assessment and risk characterization

EDI of flour-based products and cereals was assessed with the following formula:

$$EDI = \frac{C \times IR}{BW}$$

where C is the mean concentration of contaminant (mg/kg), IR is the rate of ingestion of food (g/day), BW is the body weight (kg) (mean body weights for males and females in studied regions were 77.5 and 66.1 kg, respectively).

For risk assessment MOE method was used. Risk assessors utilize the MOE to characterize the risk of exposure to genotoxic and carcinogenic chemicals that may be found in food or feed [2].

In this study MOE for Ni was calculated using the following equation:

$$MOE = \frac{HBGV}{EDI}$$

where HBGV is the up-to-date health-based guidance value of Ni, EDI is the daily intake of Ni via consumption of flour-based products.

For the chronic risk assessment, the critical effect of the increased incidence of post-implantation loss in rats observed in the one- and two-generation studies has been established for a TDI of 13µg/kg bw [4]. For the acute risk assessment, the critical effect is eczematous flare-up reactions in the skin elicited in nickel-sensitized humans after oral exposure. In the absence of a no-observed-adverse-effect-level (NOAEL), a lowest-observed-adverse-effect-level (LOAEL) of 4.3µg Ni/kg bw was used [4]. A MOE of 30 or higher would be indicative of a low health concern, MOE values lower than 30 raise a health concern for nickel-sensitized individuals, who already suffer from systemic contact dermatitis (SCD) [4].

Results and Discussion

Contents of Ni in flour-based products

The detected Ni contents are presented in Figure 1. The contents ranged from 0.0238 to 0.4286 mg/kg, with a mean of 0.2011mg/kg.

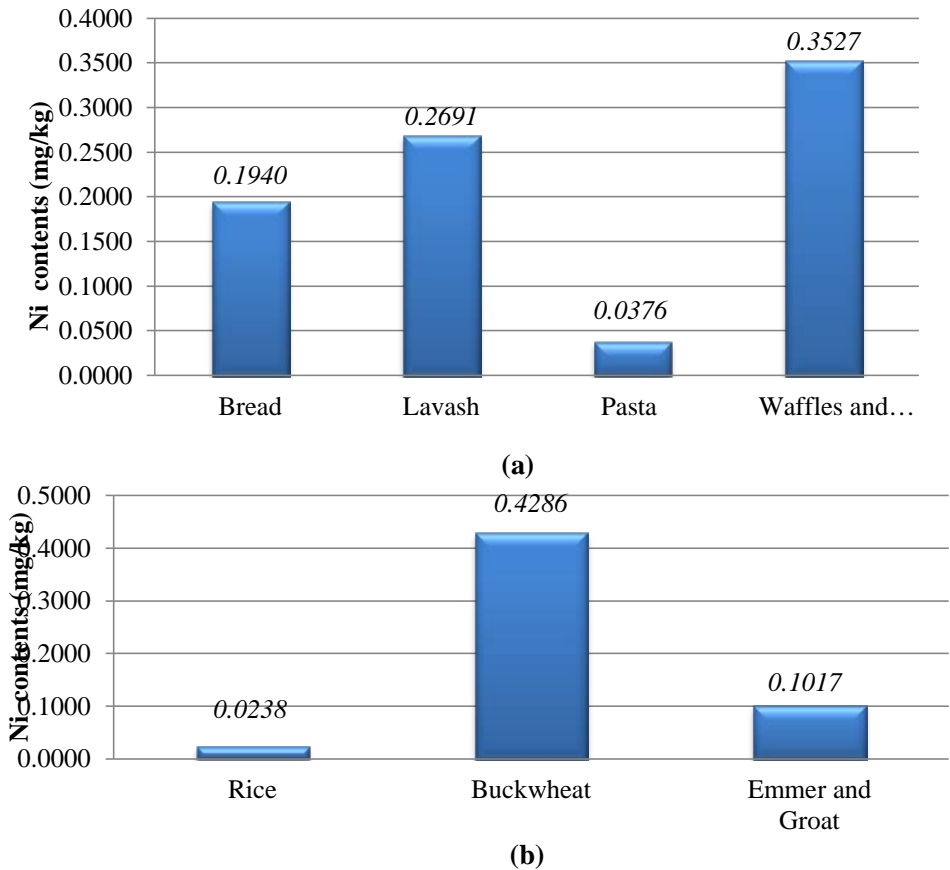


Fig.1. Ni contents (mg/kg) in flour-based products (a) and cereals (b)

To make a comparison with the study results of other countries, it can be highlighted that Ni mean content in rice samples collected from Jhenaidah and Kushtia districts of Bangladesh is 4.47 ± 2.56 mg/kg bw day [8]. This content is remarkably higher than the one obtained in the present study (0.0238 mg/kg). In Turkey, the average Ni level of all bread types all of which belong to different brands and businesses were determined as 0.38 ± 0.32 mg/kg (380 ± 320 µg/kg) [1]. Compared to the results of the current study, this value exceeds the EDI of bread (0.1940 mg/kg) and lavash (0.2691 mg/kg).

EDI and MOE of Ni

Chronic daily intake values have been estimated for each region (Table 1 and 2). The EDI values range from 8.63E-06 to 5.55E-04 mg/kg bw per day, with a mean of 1.53E-04 mg/kg bw per day. The lowest value (8.63E-06 mg/kg bw per day) has been obtained in case of rice consumption in Aragatsotn region. The highest value (5.55E-04 mg/kg bw per day) has been estimated in case of bread consumption in Kotayk region.

Compared to the TDI of 13 µg/kg bw, established by European Food Safety Authority (EFSA), none of the EDI values exceed the threshold.

Table 1. EDI of Ni in all regions of Armenia for flour-based products

Regions	EDI, mg/kg bw per day			
	Bread	Lavash	Pasta	Waffles and cookies
Yerevan	3.49E-04	2.54E-04	2.71E-05	5.72E-05
Aragatsotn	4.11E-04	2.70E-04	2.73E-05	2.39E-05
Ararat	3.26E-04	3.57E-04	2.99E-05	3.64E-05
Armavir	3.65E-04	2.85E-04	3.29E-05	4.36E-05
Gegharkunik	4.28E-04	3.39E-04	2.81E-05	3.22E-05
Lori	3.51E-04	2.31E-04	3.43E-05	2.69E-05
Kotayk	5.55E-04	2.74E-04	2.97E-05	3.68E-05
Shirak	3.90E-04	3.11E-04	2.78E-05	5.25E-05
Syunik	4.45E-04	3.15E-04	2.65E-05	3.14E-05
VayotsDzor	4.89E-04	3.52E-04	2.94E-05	0.00E+00
Tavush	3.58E-04	2.17E-04	2.95E-05	4.16E-05
MEAN	3.88E-04	2.82E-04	2.87E-05	4.68E-05

Table 2. EDI of Ni in all regions of Armenia for cereals

Regions	EDI, mg/kg bw per day		
	Rice	Buckwheat	Emmer and Groat
Yerevan	1.27E-05	2.37E-04	1.53E-05
Aragatsotn	8.63E-06	2.18E-04	1.21E-05
Ararat	1.23E-05	2.19E-04	1.34E-05
Armavir	1.89E-05	2.46E-04	1.61E-05
Gegharkunik	9.63E-06	2.24E-04	1.42E-05
Lori	1.43E-05	2.28E-04	1.31E-05
Kotayk	1.32E-05	2.60E-04	1.57E-05
Shirak	1.32E-05	2.66E-04	1.40E-05
Syunik	1.34E-05	2.35E-04	1.31E-05
VayotsDzor	1.24E-05	2.42E-04	1.48E-05
Tavush	0.00E+00	3.27E-04	0.00E+00
MEAN	1.27E-05	2.43E-04	1.48E-05

The EDI values of Ni through the intake of flour-based products and cereals have also been estimated for each gender and are presented in Figure 2. Among female consumers, the highest EDI value was equal to 3.79E-04 mg/kg bw per day in case of bread consumption, while the lowest EDI value was equal to 1.29E-05 mg/kg bw per day in case of rice consumption. A similar picture was obtained for males. Both the highest (3.79E-04 mg/kg bw per day) and lowest (1.29E-05 mg/kg bw per day) EDI values were obtained in case of the intake of rice and bread, respectively.

(b)

Fig.2. EDI of Ni for man and female for flour-based products (a) and cereals (b)

For acute risk assessment, MOE has been calculated and is represented in Table 3 and 4. As indicated, the magnitude of MOE ranged from 3.76 to 142.33. MOEs lower than 30 have been calculated in all the regions for the following products: 'bread', 'lavash', 'buckwheat', and 'emmer and groat'. For 'waffles and cookies' MOEs lower than 30 have been obtained only in Yerevan, Armavir, Shirak, and Tavush. In case of pasta intake, the MOEs were lower than 30 only in Armavir and Lori regions, while in other regions MOEs were slightly above 30 (31.22 - 35.24). Only for rice, the MOE values were substantially higher than 30 in all the regions, indicating no possible health risks.

Table 3. MOE of Ni in all regions of Armenia for flour-based products

Regions	MOE			
	Bread	Lavash	Pasta	Waffles and cookies
Yerevan	12.31	16.94	34.55	21.49
Aragatsotn	10.46	15.95	34.24	51.43
Ararat	13.20	12.04	31.22	33.74
Armavir	11.78	15.08	28.42	28.16
Gegharkunik	10.05	12.68	33.23	38.19
Lori	12.25	18.61	27.27	45.60
Kotayk	7.75	15.67	31.49	33.36
Shirak	11.03	13.82	33.57	23.41
Syunik	9.65	13.66	35.24	39.10
VayotsDzor	8.79	12.23	31.80	-
Tavush	12.00	19.83	31.72	29.55
MEAN	11.08	15.23	32.52	26.23

Note – ' - ' Consumption of this product is absent in the given region due to the limited number of consumers.

Table 4. MOE of Ni in all regions of Armenia for cereals

Regions	MOE		
	Rice	Buckwheat	Emmer and Groat
Yerevan	96.65	5.18	20.04
Aragatsotn	142.33	5.64	25.29
Ararat	100.13	5.61	22.97
Armavir	65.17	5.00	19.13
Gegharkunik	127.53	5.50	21.68
Lori	85.69	5.39	23.40
Kotayk	93.11	4.72	19.54
Shirak	93.04	4.62	21.93
Syunik	91.68	5.22	23.43
VayotsDzor	99.06	5.08	20.73
Tavush	-	3.76	-
MEAN	96.40	5.06	20.76

Note – ' - ' Consumption of this product is absent in the given region due to the limited number of consumers.

Fig. 3 includes MOE values calculated for each product and gender. The MOE values range from 4.67 to 96.86, with a mean of 29.55. Both for males and females, MOE values lower than 30 have been obtained in case of the intake of 'bread', 'lavash', 'groat and emmer', and 'waffles and cookies'.

(b)

Fig. 3. MOE for male and female for flour-based products (a) and cereals (b)

For the remaining food products, the calculated MOE values were within the acceptable threshold (> 30). It is noteworthy that, in the case of the EDI, the highest value has been obtained for bread, meanwhile, in case of the MOE, the highest possible risk has been obtained for buckwheat.

Conclusion

In Armenia, flour-based products and cereals are characterized with a frequent consumption; particularly bread and lavash are consumed daily. Therefore, these products have an essential contribution to the intake of Ni in Armenia. This study presents the results of the risk assessment of Ni via consumption of flour-based products and cereals among the adult population of Armenia using a MOE approach.

For all the studied products, none of the EDI values of Ni exceed the TDI. However, in all the regions of Armenia, MOEs lower than 30 have been obtained for 'bread', 'lavash', 'buckwheat', and 'emmer and groat'. In case of pasta intake, the MOEs were lower than 30 only in Armavir and Lori regions. For 'waffles and cookies' MOEs lower than 30 have been obtained only in Yerevan, Armavir, Shirak, and

Tavush. These values of MOE are indicative of a plausible health risk for Ni sensitized individuals who suffer from systemic contact dermatitis. Only for rice, the MOE values were substantially higher than 30 in all the regions, indicating no possible health risks.

Considering that health risks may arise not only through the consumption of Ni contaminated products, but also via the intake of other products contaminated with Ni or other toxic elements, it is suggested to include other toxic heavy metals or trace elements as well as other commonly consumed food items for future investigations.

References

1. Başaran, B. (2022). Comparison of heavy metal levels and health risk assessment of different bread types marketed in Turkey. *Journal of Food Composition and Analysis*, 104443.
2. EFSA (2019). Risk evaluation of chemical contaminants in food in the context of RASFF notifications: Rapid Assessment of Contaminant Exposure tool (RACE) (Vol. 16, No. 5, p. 1625E).
3. EFSA/FAO/WHO. (2011). Towards a harmonised Total Diet Study approach: a guidance document. *EFSA Journal*, 9 (11), 2450, 66.
4. European Food Safety Authority (EFSA). EFSA Panel on Contaminants in the Food Chain (CONTAM). (2020). Update of the risk assessment of Ni in food and drinking water. *EFSA Journal*, 18(11), e06268. DOI: 10.2903/j.efsa.2020.6268
5. Genchi, G., Carocci, A., Lauria, G., Sinicropi, M. S., and Catalano, A. (2020). Ni: Human health and environmental toxicology. *International journal of environmental research and public health*, 17(3), 679.
6. International Agency for Research on Cancer (IARC). (2012). Ni and Ni Compounds, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100C. Lyon, France: World Health Organization, Available at: <https://publications.iarc.fr/120>
7. Jitaru, P., Ingenbleek, L., Marchond, N., Laurent, C., Adegboye, A., Hossou, S.E., Kone, A. Z., Oyedele, A.D., Kisito, C.S.K., Demb'el'e, Y.K., Eyangoh, S., Verger, P., Le Bizec, B., Leblanc, J., Guérin, T. (2019). Occurrence of 30 trace elements in foods from a multi-centresub-saharanafrica total diet study: focus on Al, as, Cd, Hg, and Pb. *Environment international*, 133, 105197. <https://doi.org/10.1016/j.envint.2019.105197>.
8. Kormoker, T., Proshad, R., Islam, M. S., Shamsuzzoha, M., Akter, A., and Tusher, T. R. (2021). Concentrations, source apportionment and potential health risk of toxic metals in foodstuffs of Bangladesh. *Toxinreviews*, 40(4), 1447-1460.
9. Mazinianian, N., Hedberg, Y., and Wallinder, I. O. (2013). Ni release and surface characteristics of fine powders of Ni metal and Ni oxide in media of relevance for inhalation and dermal contact. *Regulatory Toxicology and Pharmacology*, 65(1), 135-146.

10. More, S. L., Kovochich, M., Lyons-Darden, T., Taylor, M., Schulte, A. M., and Madl, A. K. (2021). Review and Evaluation of the Potential Health Effects of Oxidic Ni Nanoparticles. *Nanomaterials*, 11(3), 642.
11. Pintowantoro, S., Pasha, R. A. M., and Abdul, F. (2021). Gypsum utilization on selective reduction of limonitic laterite nickel. *Results in Engineering*, 12, 100296.
12. Pipoyan, D., Beglaryan, M., Sireyan, L., and Merendino, N. (2019). Exposure assessment of potentially toxic trace elements via consumption of fruits and vegetables grown under the impact of Alaverdi's mining complex. *Human and Ecological Risk Assessment: An International Journal*, 25(4), 819-834.
13. Pipoyan, D., Hovhannisyan, A., Beglaryan, M., Stepanyan, S., and Mantovani, A. (2020b). Risk assessment of dietary exposure to potentially toxic trace elements in emerging countries: A pilot study on intake via flour-based products in Yerevan, Armenia. *Food and Chemical Toxicology*, 146, 111768.
14. Pipoyan, D., Stepanyan, S., Beglaryan, M., Stepanyan, S., Asmaryan, S., Hovsepyan, A., and Merendino, N. (2020a). Carcinogenic and non-carcinogenic risk assessment of trace elements and POPs in honey from Shirak and Syunik regions of Armenia. *Chemosphere*, 239, 124809.
15. Riedel, F., Aparicio-Soto, M., Curato, C., Thierse, H. J., Siewert, K., and Luch, A. (2021). Immunological Mechanisms of Metal Allergies and the Nickel-Specific TCR-pMHC Interface. *International Journal of Environmental Research and Public Health*, 18(20), 10867.
16. Shahzad, B., Tanveer, M., Rehman, A., Cheema, S. A., Fahad, S., Rehman, S., and Sharma, A. (2018). Nickel; whether toxic or essential for plants and environment-A review. *Plant physiology and biochemistry*, 132, 641-651.
17. Statistical Committee (SC). (2020). Statistical committee RA. Available at: https://armstat.am/file/article/sv_12_20a_6200.pdf