MUTAGENIC ELEMENTS IN MILK AND MILK PRODUCTS OF TWO BRANDS ON THE SLOVAK MARKET

Robert Toman*, Martina Pšenková, Šimon Mikláš, Vladimír Tančin, Simona Almášiová

Institute of Animal Husbandry, Slovak University of Agriculture, Tr. Andreja Hlinku 2, Nitra 94976, Slovak Republic

Abstract

The aim of the work was to determine the concentration of mutagenic elements arsenic (As), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), manganese (Mn), nickel (Ni), lead (Pb), and selenium (Se) in various types of milk and dairy products from two manufacturers from the supermarket in Slovakia. The samples were analyzed by inductively coupled plasma optical emission spectrometry (ICP-OES) monthly for six months. Cd was below the level of detection in all products and the same for Cr in all types of milk. In the cheese, we found significant differences between the producers in the concentration of Mn, Cu, Cr, and Se. In other dairy products, we have found differences in the concentration of Se and Cu between producers of creamy white yogurt. Some of the elements were present in concentrations that, given the nature of the metals, could be hazardous. Arsenic in butter reached 2.244 and 2.603 mg/kg, which are very close to the limits and within the range of concentrations causing cancer. Cr concentrations in molten cheese were at the TDI level at normal daily consumption of 50 g of cheese and Pb values of 0.032 mg/kg in UHT whole milk exceeded the limit set by the European Commission (EC). Other elements do not pose any risk with the regular intake of these products. In the case of Co, Cu, Fe, and Mn they rather occurred in low concentrations. The concentration of Se in UHT semi-skimmed milk represents up to 500% of the daily requirement for an adult. Relationships between individual elements in milk and dairy products are rare in the literature. Therefore, the results of the work will contribute to the knowledge in this area. Several significant strong correlations between elements were found. The most common correlations were between Fe, Cu, and Ni. As milk and dairy products are among the staple foods consumed by the most vulnerable groups of people, namely children and the elderly, their presence in milk and dairy products needs to be monitored.

Keywords: *mutagens, metals, chemical elements, milk, dairy products, Slovakia*

1. INTRODUCTION

Dairy products, including milk, are an important part of a healthy diet for humans. These foods contain many important nutritional elements like calcium, magnesium, phosphorus, potassium, selenium, vitamins, and other compounds (Gaucheron 2005, 2011). Cow's milk is widely used for children's nutrition and its nutrients are needed for their growth and mental development (Ribeiro Sant'Ana, de Carvalho & da Silva 2021). Its consumption improves the calcium and vitamin B12 status of school children (Kumar et al. 2021) and the cognitive and physical performance of young children (Kuriyan et al. 2016). Therefore, the main concern in the milk production and dairy industry is the safety of these food sources. Increasing industrial activities, growing agriculture, and other human activities contribute to the environmental pollution by many xenobiotics, including metals (Briffa et al. 2020; Page et al. 2014; Onakpa et al., 2018). These metals then occur in the food chain and are transferred in the following direction: feed - animal - raw milk - dairy products - human. Many of these chemical elements cause toxic effects on humans even at low concentrations, such as cadmium (Barbier et al. 2005; Cobbina et al. 2015a; Kumar & Sharma 2019; Vassallo et al. 2020), lead (Barbier et al. 2005; Cobbina et al. 2015a; Vassallo et al. 2020; Javorac et al. 2021, 2022), arsenic (Cobbina et al. 2015a), thallium (Campanella et al. 2019), mercury (Barbier et al. 2005; Fernandes Azevedo et al. 2012; Cobbina et al. 2015; Vassallo et al. 2020), manganese (Batschauer et al. 2021), and chromium (Barbier et al. 2005; Haney 2015). In addition, the combined effect of several metals that may be present in raw material or food needs to be taken into account (Cobbina et al. 2015b, 2015c; Wu et al. 2016; Fan, Zhou & Feng 2017). In some cases, the consumption of cow's milk and dairy products can be risky. As Sobhanardakani (2018) warns,

due to the higher contamination of raw and pasteurized cow's milk with cadmium, lead and zinc, the heavy metal content should be controlled throughout the milk processing. Pipoyan et al. (2022) warn of the health risk of Cd and Pb intake through dairy products (pasteurized milk, sour cream, matsoun, and cow's milk cheese) in Armenia. Dairy products in the sales network in Brazil can be considered as sources of heavy metals such as Cu, Hg, Ni, Pb, and Se. Children are the main risk group in Sao Luis because they consume mainly Pb and Hg in these products (Ribeiro Sant'Ana, de Carvalho & da Silva 2021). The occurrence of Cd, Cu, Pb, and Zn in various types of milk was also confirmed by Tripathi et al. (1999). In this case, however, the concentration of toxic elements did not reach the permitted limits, but significantly lower values than the recommended limits were also recorded for the essential elements.

In addition to various toxic effects, some metals and metalloids can also cause damage to genetic information and mutagenesis. These mutagens can persist in the environment for a long time after entering the soil and then enter the animal body (Čėsnienė et al. 2017). In addition, the genotoxic effects of these metals, such as Cd, Pb, and Cr, can lead to carcinogenesis (Reutova 2017; Leelapongwattana & Bordeerat 2020). Permanent changes in genetic information caused by mutagens have stimulated the development of research into the testing and molecular mechanisms of heavy metal mutagenicity (Eastmond et al. 2009; Koedrith et al. 2013), as well as monitoring of these substances in the environment and food (Kocadal et al. 2021; Tunegová et al. 2018). Heavy metals can act genotoxically in various ways. Arsenic inhibits DNA renewal, directly damages DNA, and induces chromosomal aberrations (Jha et al. 1992; Zhou & Xi 2018). Cadmium, like arsenic, is a weak mutagen, but it causes oxidative stress and damages DNA (Mohamed 2021) and increases the frequency of chromosomal aberrations (Abrahim et al. 2011). Hexavalent chromium compounds are considered mutagenic and carcinogenic, but their mechanism of action also includes trivalent metabolite Cr(III), which binds to DNA (Brown et al. 2020). In addition, oxidative damage has been found to cause the genotoxic effects of chromium and chromosome damage even at doses that show low cytotoxicity (Wise, Wise & Little 2002). Lead exposure causes an increase in the level of aminolevulinic acid (ALA) in the blood, which causes the formation of ROS (8-hydroxy-2′-deoxyguanosine). The result is DNA damage. These genotoxic effects of lead have been observed in workers at a wastewater treatment plant in Iraq (Ibrahem et al. 2020). Besides the toxic elements, some essential elements such as iron, selenium, copper, and manganese can also be genotoxic. An increase in lipid peroxidation and a decrease in the activity of the antioxidant system in the rat spleen were found after ingestion of a mixture of As, Cd, Cr, Fe, Hg, Mn, Ni, and Pb (Jadhav, Sarkar & Tripathit 2006). Metals such as Co, Cr, Cu, and Fe can cause the production of reactive radicals and oxidative stress. Increased ROS production causes DNA damage, which can ultimately lead to carcinogenesis (Jomova & Valko 2011).

Given the nutritional importance of the consumption of milk and dairy products, especially for the child population, the main goal was to determine the levels of ten mutagenic elements in milk and various dairy products in Slovakia commonly available in the retail network. We compared the concentrations of these elements in the products of two Slovak producers and we also found the correlation relationships between the individual elements in the analyzed products.

2. MATERIALS AND METHODS

2.1. Sample collection

Samples of various 16 dairy products and milk were taken in supermarkets in Nitra, Slovakia, regularly at monthly intervals during the first half of 2021. Each month (a total of 6 times) the following samples of milk and milk products were obtained: ultra-high temperature (UHT) semi-skimmed milk, UHT whole milk, pasteurized semi-skimmed milk, whole pasteurized milk, creamy white yogurt, acidophilic white whole milk, Eidam cheese 45%, steamed cheese, whipping cream, soft lump curd, cream spread, steamed smoked cheese, sour cream, molten cheese, sheep cheese (bryndza), and butter. The same products came from two different Slovak manufacturers, a total of 32 products.

The entire package available in the store was frozen in the original packaging until processing at -18°C. After thawing, the dairy product samples were homogenized with a manual homogenizer Diax 600

(Heidolph, Germany). Approximately 2 ml of liquid products and 2 g of solid products were collected for analysis of the content of selected mutagenic metals and metalloids.

2.2. Sample analysis

Ten mutagenic elements (As, Cd, Co, Cr, Cu, Fe, Mn, Ni, Pb, and Se) were analyzed in all samples of milk and dairy products by inductively-coupled plasma optical emission spectrometry (ICP-OES). Before the analysis, the samples were mineralized in the high-performance microwave digestion system Ethos UP (Milestone Srl, Sorisole, BG, Italy) in a solution of 5 mL HNO3 ≥69.0% (TraceSELECT®, Honeywell Fluka, Morris Plains, USA), 1mL H2O2 ≥30%, for trace analysis (Sigma Aldrich, Saint – Louis, Missouri, USA) and 2mL of ultrapure water (18.2 MΩ cm-1; 25 °C, Synergy UV, Merck Millipore, France). The sample digestion by the manufacturer consisted of heating and cooling phases. The samples were first warmed to 200 °C for 15 min and this temperature was maintained for another 15 min. Then the samples were cooled for 15 min to reach the temperature of 50 °C. The digests were filtered through the VWR Quantitative filter paper 454 (particle retention 12 – 15 μm) (VWR International, Leuven, France) into the volumetric flasks and filled up with ultrapure water to a volume of 50 mL. Analysis of the elements was carried out using an inductively coupled plasma - optical emission spectrometer (ICP OES 720, Agilent Technologies Australia (M) Pty Ltd.) with axial plasma configuration and with auto-sampler SPS-3 (Agilent Technologies, Switzerland).

The operating parameters of determination of elements by ICP-OES were as follows: RF power 1.30 kW, plasma flow 15.0 L/min, auxiliary flow 1.50 L/min, nebulizer flow 0.85 L/min, replicated read time 5 s, instrument stabilization 15 s, sample uptake delay 25 s, pump rate 15 rpm, rinse time 10 s.

The wavelengths (λ/nm) for individual elements were as follows: As 188.980, Fe 234.350, Cd 226.502, Mn 257.610, Co 228.615, Ni 231.604, Cr 267.716, Pb 220.353, Cu 324.754, and Se 196.026.

2.3. Statistical analysis

Statistical analysis of the data was performed using Statistica Cz version 10 (TIBCO Software, Inc., Palo Alto, CA, USA). Differences in concentrations of the analyzed elements in milk between the seasons were compared by the ANOVA and Student's t-test. All data were expressed as mean and standard deviation. The relationships between the concentrations of metals in the milk and dairy products were calculated using Pearson's correlation analysis. A probability level of $p<0.05$ was considered statistically significant.

3. RESULTS

Table 1 summarizes the results of the different types of milk and milk drinks. The analysis shows that there were no significant differences between the two producers. In addition, cadmium and chromium were below the level of detection in all products. Lead was found only in the UHT whole milk sample of producer 1. Moreover, we did not detect the presence of As and Se in pasteurized semi-skimmed milk from both producers. In the case of whole pasteurized milk of both producers, we did not find any selenium. We found the highest concentrations of As in UHT semi-skimmed milk of producer 2, cobalt in UHT semi-skimmed milk and pasteurized semi-skimmed milk of manufacturer 2, copper in UHT semi-skimmed milk of manufacturer 2, iron in pasteurized semi-skimmed milk of manufacturer 1, manganese in UHT semi-skimmed milk of manufacturer 2, nickel in whole pasteurized milk of manufacturer 2, and selenium in UHT semi-skimmed milk of producer 2.

Table 1. Concentrations of analyzed mutagenic elements in milk and milk drinks (mg/kg)

	UHT Semi-skimmed milk		**UHT Whole milk**		**Pasteurized semi-skimmed milk**	
	Producer 1	Producer 2	Producer 1	Producer 2	Producer 1	Producer 2
	Mean ± SD					
As	0.049±0.119	0.275±0.319	0.109±0.266	ND	ND	ND
Cd	ND	ND	ND	ND	ND	ND
Co	ND	0.011±0.027	0.010±0.017	0.006±0.014	0.006±0.015	0.011±0.020
Cr	ND	ND	ND	ND	ND	ND
Cu	0.015±0.037	0.175±0.186	0.147±0.172	0.168±0.190	0.166±0.167	0.155±0.143
Fe	0.101±0.115	0.717±1.115	0.514±0.484	0.695±0.659	0.765±0.094	0.745±0.041
Mn	0.017±0.011	0.033±0.060	0.008±0.007	0.019±0.017	0.014±0.022	0.019±0.020
Ni	0.040±0.099	0.068±0.083	0.026±0.041	0.110±0.147	0.117±0.170	0.134±0.193
Pb	ND	ND	0.032±0.078	ND	ND	ND
Se	0.293±0.534	ND	ND	0.096±0.233	ND	ND

	Whole pasteurized milk		**Acidophilic white whole milk**	
	Producer 1	Producer 2	Producer 1	Producer 2
	Mean ± SD			
As	0.110±0.269	0.089±0.156	0.138±0.219	0.120±0.199
Cd	ND	ND	ND	ND
Co	0.009±0.023	0.002±0.005	0.008±0.020	0.003±0.008
Cr	ND	ND	ND	ND
Cu	0.119±0.132	0.158±0.161	0.140±0.117	0.168±0.194
Fe	0.554±0.565	0.868±0.130	0.620±0.699	0.526±0.433
Mn	0.007±0.006	0.019±0.015	0.013±0.012	0.014±0.011
Ni	0.067±0.125	0.267±0.444	0.057±0.093	0.074±0.083
Pb	ND	ND	ND	ND
Se	ND	ND	ND	0.232±0.383

ND – not detected; SD – standard deviation

Table 2 shows the results of analyzes of six types of cheese from two producers. As in the case of milk, cadmium was below the detection limit in cheeses. Chromium was below the detection limit in Eidam cheese 45% and soft lump curd of both manufacturers. Unlike milk, we also found significant differences in the concentration of some elements between the two producers. Significantly higher ($p<0.001$) manganese concentration was found in Eidam cheese 45% of producer 1. Significantly higher ($p<0.05$) copper concentration was recorded in steamed cheese as well as chromium and selenium in molten cheese of producer 1. In addition, a higher ($p<0.05$) concentration of copper and manganese in molten cheese of producer 2 was found. In cheeses, arsenic, iron, and nickel were found in the highest concentration in steamed smoked cheese of producer 1. Even in the case of cobalt, copper, manganese, and lead, the highest concentrations were found in Eidam cheese 45%, and chromium in molten cheese

of producer 1. In cheese of producer 2, the highest concentration of all cheeses analyzed was found for selenium in steamed cheese.

Table 2. Concentrations of analyzed mutagenic elements in cheese (mg/kg)

	Eidam cheese 45%		**Steamed cheese**		**Soft lump curd**	
	Producer 1	Producer 2	Producer 1	Producer 2	Producer 1	Producer 2
	Mean ± SD					
As	0.576±0.656	0.804±0.949	0.621±0.495	0.787±0.574	0.220±0.287	0.080±0.196
Cd	ND	ND	ND	ND	ND	ND
Co	0.040±0.046	0.024±0.040	ND	0.015±0.023	ND	0.007±0.017
Cr	ND	ND	0.019±0.030	0.039±0.031	ND	ND
Cu	0.587±0.247	0.431±0.237	0.433±0.256	0.108±0.104*	0.518±0.342	0.468±0.225
Fe	1.284±0.886	1.682±1.496	1.209±0.788	0.535±0.334	0.949±0.822	1.170±0.835
Mn	0.284±0.033	0.135±0.026***	0.124±0.021	0.149±0.010	0.064±0.021	0.079±0.031
Ni	0.255±0.293	0.196±0.230	0.238±0.389	0.057±0.089	ND	0.033±0.081
Pb	0.152±0.265	ND	ND	0.131±0.251	0.117±0.184	0.111±0.177
Se	0.566±0.651	0.746±0.824	0.517±0.701	1.750±1.255	0.119±0.290	0.297±0.460
	Steamed smoked cheese		**Molten cheese**		**Sheep cheese (bryndza)**	
	Producer 1	Producer 2	Producer 1	Producer 2	Producer 1	Producer 2
	Mean ± SD					
As	1.204±0.336	1.149±0.409	0.730±0.495	0.756±0.395	0.776±0.617	0.593±0.663
Cd	ND	ND	ND	ND	ND	ND
Co	0.007±0.017	0.016±0.034	0.012±0.030	0.007±0.018	0.014±0.034	0.017±0.033
Cr	0.007±0.018	0.018±0.031	0.098±0.055	0.023±0.046*	0.003±0.009	0.006±0.014
Cu	0.421±0.271	0.350±0.190	0.029±0.045	0.313±0.257*	0.445±0.493	0.389±0.344
Fe	1.822±1.054	1.402±1.763	0.462±0.344	1.055±0.740	1.136±0.567	0.946±0.612
Mn	0.127±0.064	0.093±0.051	0.104±0.010	0.130±0.021*	0.150±0.044	0.143±0.018
Ni	0.445±0.671	0.256±0.629	ND	0.018±0.045	0.051±0.125	0.019±0.047
Pb	0.132±0.204	0.091±0.162	0.067±0.163	0.067±0.163	0.088±0.161	0.067±0.163
Se	1.130±0.747	0.788±0.721	1.585±0.916	0.381±0.445*	0.961±0.635	1.081±0.388

ND – not detected; SD – standard deviation; *p<0.05, ***p<0.001

The results of the analyzes of other dairy products of both producers are shown in Table 3. The results show that a significant difference in the concentration of elements between the two producers was recorded only in the case of creamy white yogurt. We found a significantly higher ($p<0.05$) copper concentration in the product of producer 1 and selenium in the yogurt of producer 2. We also found the occurrence of cadmium below the detection limit in these dairy products. Chromium was not found in any of the manufacturers of whipping cream and creamy white yogurt. We found cobalt below the

detection limit in both producers only in the case of cream spread. Arsenic and lead were found in the highest concentration in butter and manganese in a cream spread of producer 2. The highest concentrations of Cu, Fe, Ni, and Se were found in the butter of producer 1. Cobalt was found in the highest amount in creamy white yogurt and chromium in sour cream as well in both producers.

Table 3. Concentrations of analyzed mutagenic elements in milk creams and other dairy products (mg/kg)

	Whipping cream		**Sour cream**		**Creamy white yogurt**	
	Producer 1	Producer 2	Producer 1	Producer 2	Producer 1	Producer 2
	Mean ± SD					
As	1.159±0.365	1.188±0.454	0.733±0.535	0.405±0.515	0.222±0.269	0.229±0.257
Cd	ND	ND	ND	ND	ND	ND
Co	ND	0.007±0.019	0.005±0.012	0.004±0.009	0.016±0.040	0.016±0.040
Cr	ND	ND	0.012±0.030	0.012±0.030	ND	ND
Cu	0.172±0.150	0.270±0.350	0.153±0.143	0.153±0.162	0.255±0.259	0.005±0.013*
Fe	0.893±0.085	0.691±0.781	0.806±0.641	0.445±0.451	0.819±0.103	0.250±0.271
Mn	0.008±0.011	0.024±0.014	0.023±0.031	0.017±0.012	0.011±0.012	0.025±0.010
Ni	0.249±0.381	0.048±0.119	0.043±0.069	0.018±0.044	0.092±0.119	0.030±0.074
Pb	0.067±0.163	0.132±0.204	0.093±0.162	0.067±0.163	ND	0.060±0.100
Se	1.055±0.300	1.046±0.288	0.653±0.554	0.480±0.543	0.066±0.103	0.736±0.599*

	Cream spread		**Butter**	
	Producer 1	Producer 2	Producer 1	Producer 2
	Mean ± SD			
As	0.958±0.556	1.089±0.555	2.244±1.139	2.603±0.535
Cd	ND	ND	ND	ND
Co	ND	ND	0.005±0.014	0.008±0.014
Cr	0.001±0.003	ND	ND	0.009±0.022
Cu	0.293±0.393	0.321±0.359	0.375±0.919	0.302±0.349
Fe	1.100±0.185	1.096±0.341	1.608±0.940	1.558±0.711
Mn	0.029±0.013	0.054±0.037	0.051±0.099	0.008±0.013
Ni	0.028±0.069	0.141±0.191	0.289±0.158	0.084±0.207
Pb	0.067±0.163	0.095±0.164	0.067±0.163	0.141±0.200
Se	0.923±0.520	1.450±0.510	4.102±3.240	2.623±1.310

ND – not detected; SD – standard deviation; *p<0.05

Since there are also interactions between chemical elements, we found correlations between all elements in individual products. The analysis showed that iron and copper were most often in a statistically significant strong correlation. Other frequent statistically strong correlations were found between Fe and

Ni, as well as between Cu and Ni. In UHT semi-skimmed milk, we found a strong positive correlation relationship between Fe:Mn in both producers ($r=0.818$, $p<0.05$, $r=0.923$, $p<0.01$, respectively). In the case of producer 2, we found a strong positive correlation between Fe:Cu ($r=0.852$, $p<0.05$), Fe:Ni ($r=0.935$, $p<0.01$), and Cu:Ni ($r=0.970$, $p<0.01$). In UHT whole milk, we found a lower number of correlations. In both producers, a strong positive correlation was found between Fe:Cu ($r=0.818$, $p<0.05$, $r=0.848$, $p<0.05$, respectively), Fe:Ni in producer 1 ($r=0.813$, $p<0.05$) and Cu:Ni in producer 2 ($r=0.892$, $p<0.05$). In pasteurized semi-skimmed milk of both producers, a strong positive correlation was found between Fe:Ni ($r=0.994$, $p<0.01$, $r=0.985$, $p<0.01$, respectively) and between Fe:Cu ($r=0.844$, $p< 0.05$), Fe:Mn ($r=0.814$, $p<0.05$), and Cu:Ni ($r=0.878$, $p<0.05$) in producer 2. In whole pasteurized milk, a strong positive correlation relationship was found between Fe:Cu in producer 1 ($r=0.922$, $p<0.01$) and between As:Co ($r=0.925$, $p<0.01$) in producer 2. On the other hand, in acidophilic white whole milk, we did not find any significant correlations between the observed elements.

In the cheese category of both producers, we found statistically strong correlations between Fe:Ni ($r=0.930$, $p<0.01$, $r=0.923$, $p<0.01$, respectively). Other significant strong positive correlations were found in this cheese in producer 2, namely between Cr:As ($r=0.856$, $p<0.05$), Cr:Mn ($r=0.837$, $p<0.05$), As:Mn ($r=0.824$, $p<0.05$), and Cu:Ni ($r=0.873$, $p<0.05$). In steamed cheese of producer 1, a strong positive correlation between Fe:Cu ($r=0.989$, $p<0.01$) and a strong negative correlation between As:Cu ($r=-0.840$, $p<0.05$) were found. In producer 2, we found a strong positive correlation between Co:Cu ($r=0.818$, $p<0.05$) and a strong negative correlation between Co:Mn ($r=-0.868$, $p<0.05$). In soft lump curd, we found a strong positive correlation between Cu:Se in producer 1 ($r=0.881$, $p<0.05$). In this product of producer 2, we observed a strong positive correlation between Cu:Fe ($r=0.877$, $p<0.05$) and Pb:Se ($r=0.986$, $p<0.01$). A strong negative correlation was found between Cu:Mn ($r=-0.913$, $p<0.05$). In steamed smoked cheese, we found a strong positive correlation between Cu:Ni in producer 1 ($r=0.893$, $p<0.05$). In the case of producer 2, we calculated strong positive correlations between As:Pb ($r=0.853$, $p<0.05$), Cr:Pb ($r=0.991$, $p<0.01$), and Fe:Ni ($r=0.935$, $p<0.01$). We recorded a higher number of correlations in molten cheese. In this cheese of producer 1, strong negative correlations were found between Co:Cr (r -0.870, $p<0.05$), Co:Se ($r=-0.847$, $p<0.05$), Cu:Cr ($r=-0.903$, $p< 0.05$), and Cu:Se ($r=-0.878$, $p<0.05$). In contrast, we found strong positive correlations between Co:Cu ($r=0.902$, $p<0.05$), Mn:Pb ($r=0.877$, $p<0.05$), and Cr:Se ($r=0.996$, $p<0.01$). Strong positive correlations between As:Mn ($r=0.958$, $p<0.01$), Cr:Pb ($r=0.977$, $p<0.01$), and Fe:Cu ($r=0.953$, $p<0.01$) were calculated in producer 2. In sheep cheese (bryndza) we found strong positive correlations between Cr:Mn ($r=0.855$, $p<0.05$, $r=0.814$, $p<0.05$, respectively) at both producers. In this product of producer 1 we further found a strong positive correlation between Cr:Pb ($r=0.947$, $p<0.01$). For producer 2, the same relationships were recorded for As:Se ($r=0.855$, $p<0.05$) and Pb:Mn ($r=0.824$, $p<0.05$).

We found more correlations in milk creams and other dairy products like yogurts, creams, spreads and butter. In whipping cream, we found strong positive correlations between Fe:Cu in both manufacturers ($r=0.924$, $p<0.01$, $r=0.954$, $p<0.01$, respectively). In the case of producer 1, there were also strong positive correlations between Pb:Mn ($r=0.843$, $p<0.05$) and Pb:Se ($r=0.817$, $p<0.05$) and in producer 2 between Ni:Cu ($r=0.895$, $p<0.05$). In sour cream, we found strong positive correlations. For producer 1, these relationships were found between Cr:Pb ($r=0.923$, $p<0.01$), Fe:Se ($r=0.843$, $p<0.05$), and Mn:Ni ($r=0.892$, $p<0.05$). In producer 2, correlation relationships between As:Se ($r=0.847$, $p<0.05$) and Cu:Fe ($r=0.912$, $p<0.05$) were found. In creamy white yogurt, we also found statistically significant strong positive correlations. In the case of producer 1, the relationships between Fe:Cu ($r=0.870$, $p<0.05$), Fe:Ni ($r=0.980$, $p<0.01$), and Cu:Ni ($r=0.925$, $p<0.01$) were recorded. In yogurt of producer 2, the relationship between Fe:Mn was found ($r=0.876$, $p<0.05$). In the cream spread, we recorded strong positive correlation between Ni:Fe in both manufacturers ($r=0.825$, $p<0.05$, $r=0.958$, $p<0.05$, respectively). However, we also found a strong negative correlation between Ni:As ($r=-0.843$, $p<0.05$) in producer 1. In producer 2, we found a strong positive correlation between Cu:Mn ($r=0.893$, $p<0.05$). The last analyzed dairy product was butter with the highest number of different correlations, especially in the case of producer 1. Arsenic was in a strong negative correlations with Fe ($r=-0.965$, $p<0.01$), Cu ($r=-0.985$, $p<0.01$), Mn ($r=-0.972$, $p<0.01$), Ni ($r=-0.965$, $p<0.01$), and Se ($r=-0.895$, $p<0.05$). We found strong positive correlations in butter of producer 1 between Mn:Cu ($r=0.993$, $p<0.01$), Mn:Fe ($r=0.903$, $p<0.01$), Mn:Ni ($r=0.918$, $p<0.01$), Se:Cu ($r=0.928$, $p<0.01$), Se:Fe ($r=0.968$, $p<0.01$), Se:Mn ($r=0.928$,

p<0.01), and Se:Ni (r=0.828, p<0.01). In butter of producer 2, we found strong positive correlations between Fe:Cr (r=0.834, p<0.05), and Fe:Cu (r=0.876, p<0.05).

4. DISCUSSION

In this work, we analyzed 16 different dairy products from two Slovak producers for the presence of 10 mutagenic chemical elements over 6 months. Of all the elements monitored, only cadmium was below the level of detection in all products of both manufacturers. We consider this to be a positive finding, as cadmium is a highly toxic metal and can damage many human and animal organs and functions, even at low concentrations (Roychoudhury et al. 2010; Duranova et al. 2014; Chen et al. 2018). In addition, most of the work that analyzed cadmium in milk and dairy products found this element in these products. Capcarova et al. (2019) recorded a concentration of cadmium in cow's milk in the Slovak market at 0.27 - 0.42 mg/L. However, the analyses showed that exposure to Cd in cow's milk accounts for a low proportion of Cd Provisional Tolerable Weekly Intake (PTWI). Similar results were found in cottage cheese (Capcarova et al. 2020). Although cadmium is a relatively weak mutagen (Mohamed 2021), it is not suitable to be present in food. In addition, milk is one of the staple foods of infants and young children. Therefore, Ibrahem et al. (2020) recommend tightening regulatory measures to minimize this risk. Cadmium, together with mercury and nickel, as known mutagens, correlate strongly with an increased risk of developing autism spectrum disorders in children (Kinney et al. 2010).

Unlike Cd, arsenic was found in all products except pasteurized semi-skimmed milk from both producers and UHT whole milk of producer 1. The highest concentrations of As were found in butter from both producers up to 2,603 mg/kg. Arsenic was present in a higher concentration compared to other monitored elements in raw ewe milk from the area of Slovakia, which is considered intact in terms of environmental burden. The concentrations found in this milk (0.527 mg/kg) were significantly lower than in various types of cow's milk from the market in our work (0.049 - 275 mg/kg) (Toman et al. 2022). Sarsambayeva et al. (2020) recorded As and Hg in dairy products from Kazakhstan below the detection limit. Genotoxic analyzes of people living near the former mining area in Northern Cyprus have shown a higher incidence of micronuclei in the presence of arsenic and copper (Kocadal et al. 2021). High levels of genotoxicity and cytotoxicity in three different human cell lines (keratinocytes, melanocytes, and dendritic cells) have been found by Graham-Evans et al. (2004). Arsenic, like cadmium, cobalt, and nickel, can damage the DNA repair system even at low concentrations, which may not damage the cell itself (Hartwig et al. 2002). According to EFSA (2014), milk and dairy products are among the main sources of inorganic As for infants, and no maximum limit for As in milk has been set in the EU or Slovakia. According to EFSA CONTAM Panel (2009), the PTWI of 15 µg/kg established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is no longer appropriate However, The EFSA CONTAM Panel notes that values between 0.3 and 8 µg/kg b.w. per day were identified for lung, skin and bladder cancers (EFSA Contam Panel, 2009). Arsenic values, especially in butter in the retail network, found in our analyzes are therefore alarming.

Another metal that was only found in some products was chromium. In all types of milk, its values were below the detection limit. However, relatively high Cr concentrations of 0.382 - 0.506 µg/g were found in yak milk in China (Sun et al. 2011). Similarly, values up to 477 µg/L have been recorded in cow's milk from Sri Lanka (Diyabalanage et al. 2021). The highest concentration of Cr was recorded in samples of molten cheese. In cheeses, the incidence of Cr was below the detection limit in Eidam cheese 45% and soft lump curd of both manufacturers. We found a significant difference in the Cr level between the producers of molten cheese. Cr concentrations found by Capcarova et al. (2020) in various cottage cheese from the Slovak market were in the range of 0.08 - 0.17 mg/kg with the highest average concentrations in white cottage cheese. Our analyses showed lower concentrations in different types of cheese from two Slovak producers. Souza et al. (2019) found Cr concentrations in yogurt below the limit of detection, similar to our case. The mutagenic potential of chromium compounds has been found for both hexavalent Cr and its trivalent metabolite (Brown et al. 2020). EFSA CONTAM Panel (2014) recommended tolerable daily intake (TDI) is 0.3 mg/kg b.w. for Cr (III) in drinking water. In our study, only molten cheese from both producers contained Cr concentrations, which when consumed 50 g of cheese per day are close to the TDI. Cr concentrations of 0.035 and 0.079 mg/kg were found in two

types of cheese made from cow's milk obtained on contaminated pastures in Georgia (Al Sidawi et al. 2021). These values are within the range of our analyses.

Lead is a toxic metal that causes damage to many organs and systems in the body. The most well-known effects are hypertension, and kidney, nervous system and reproductive damage (Gidlow 2015). However, lead also has serious genotoxic and carcinogenic effects. Although the effect of Pb on DNA repair mechanisms is assumed, it means an indirect effect, its mechanism of genotoxic action is not yet quite clear (Hemmaphan & Bordeerat 2022). Lead is well absorbed, especially in children, but this depends on the amount of food intake and food ingredients (Rădulescu & Lundgren 2019). Tripathi et al. (1999) reported a daily lead intake of 1.1 µg/kg in children through baby food and indicated it below the recommended tolerable levels of 3.57 µg/kg. The authors even noted a lower incidence of lead in cow's milk than in breast milk. The occurrence of Pb in milk and dairy products has been reported by several authors. Capcarova et al. (2020) found low values of xenobiotic metals (Cd, Hg, Pb) below the permitted limit in cottage cheese from the market in Slovakia. In the case of Pb, it was in the range of 0.01 - 0.07 µg/g. The analysis concludes with a low dietary intake of these metals. Souza et al. (2019) report the occurrence of Pb in yogurt in Brazil Pb below the detection limit of 94.1 µg/g. Iwegbuel et al. (2013) recorded Pb concentrations in milk and dairy products in Nigeria of 0.002-0.40 mg/kg. In the European Union (EU), maximum lead content of 0.02 mg/kg is set only for raw milk, heat-treated milk and milk intended for the production of milk-based products (EC, 2021). In our case, we found the occurrence of lead in the category of milk and milk drinks only in samples of UHT whole milk of producer 1. The average value of Pb in this milk 0.032 mg/kg exceeded the limit set by the EC. Capcarova et al. (2019) found values of 2.62 - 3.80 µgPb/mL in the milk of Slovak and Czech producers. The authors point out that lead, like cadmium, has cumulative properties in the body and recommend monitoring these metals in milk. Meshref, Moselhy & Hassan (2014) found the highest Pb concentrations in butter (0.3285 - 0.751 ppm). In our case, the highest Pb values were found in Eidam cheese 45% and butter. Compared to the mentioned authors, the concentrations in our products were lower.

Among the monitored metals, which are considered mutagenic, we also analyzed Co, Cu, Fe, Mn, Ni, and Se. We found Co in almost all products. The highest Co values, similar to Pb, were found in Eidam cheese from both manufacturers (0.04 and 0.024 mg/kg, respectively). Slightly lower Co concentrations (0.013 and 0.03 mg/kg, respectively) were found in two types of Imeruli and Sulguni cheese from Georgia (Diyabalanage et al. 2021). In ewe milk from undisturbed area of northern Slovakia during the spring and summer season, the Co concentrations were lower (0.017 and 0.018 mg/kg, respectively) than those in our experiment (Toman et al. 2022). Co concentrations ranging from 0.46 µg/L in the Dry Zone to 12.8 µg/L in the Coconut Zone have been found in various agroclimatic zones in Sri Lanka (Al Sidawi et al. 2021). Cobalt is considered a genotoxic carcinogenic metal and causes oxidative DNA damage by ROS formation eventually by inhibition of DNA repair (Lison, van den Brule & Van Maele-Fabry 2018; Simonsen, Harbak & Bennekou 2012). Due to conflicting toxicological data on the in vivo genotoxicity of Co, the initially determined daily intake of 0.0025 µg Co/kg bw is inadequate. Therefore, EFSA's Scientific Panel on Additives and Products or Substances used in Animal Feed adopted guidance values of 0.0016 mg/kg bw and day for threshold effects of oral Co, or 0.12 mg Co for a 70-kg adult (FEEDAP 2012). The values of Co that we recorded in our analyzes in all products are low and do not pose a health risk to the consumer during normal consumption. The presence of Co in the environment and the body may be associated with the occurrence of congenital heart defects (Zhang et al. 2020). Interestingly, Co intake does not affect its concentration in the liver and blood serum, but the concentration increases in milk (Kincaid & Socha 2007). For these reasons, it is important to monitor this metal in milk and other foods that are consumed especially by pregnant women.

Despite its essentiality, copper is considered a genotoxic metal. In mutagenicity and genotoxicity tests, after administration of a subchronic Cu dose of 8.5 mg/kg to mice, the highest induction of mutagenicity was found based on the bone marrow micronucleus test (Prá et al. 2008). These data are also confirmed by toxicological analyzes in the human hepatoma HepG2 cells, where increased cytotoxicity, mutagenicity, and mitochondrial impairment occurred mainly due to copper oxide nanoparticles effects (Adeyemi et al. 2020). In addition, copper in excess intake causes Wilson's disease and neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease (Pal 2014). Copper

binds to casein in milk and can even pass from brass vessels to milk. The result may be childhood cirrhosis found in Indian children. For this reason, milk is considered an effective carrier of copper to children's enterocytes (O'Neill & Tanner 1989). The Cu concentrations we found in milk and dairy products were relatively low. According to the recommendations of EU No. 1169/2011, the daily reference intake of copper for adults is 1 mg (EP 2012). In the case of Eidam cheese, where we found the highest concentration of Cu of all dairy products, the Cu content in 100 g of cheese was 8.75% and in the case of milk 5.87% of the recommended daily copper intake for an adult. There were differences in Cu concentration between the two producers. Significantly higher concentrations were found in the case of steamed cheese and creamy white yogurt made by producer 1 and in molten cheese made by producer 2. The average incidence of Cu in cow's milk ranged from 0.120 to 0.592 mg/L and in cheeses from 1.261 to 2.463 mg/kg in Georgia (Al Sidawi et al. 2021), in cow's milk 0.008 - 0.042 ppm in Bangladesh (Muhib et al. 2016), in cheese 5.35 - 21.34 µg/g in France (Maas et al. 2011), in milk from the Czech Republic 0.95 µg/mL and from Slovakia 1.54 - 2.12 µg/mL (Capcarova et al. 2019), in cottage cheese from Slovakia 0.08 - 0.22 µg/g (Capcarová et al. 2020), and in milk 0.0953 ppm, in Kareish cheese 0.087 ppm, and butter 0.60 ppm from Egypt (Meshref, Moselhy & Hassan 2014).

Like Cu, Fe is considered a genotoxic and mutagenic metal (Prá et al. 2008). Excessive Fe intake increases the formation of hydrogen peroxide to free-radical ions and DNA damage occurs. In addition, long-term oxidative stress can affect Fe uptake and storage and subsequent cytotoxic and mutagenic changes (Emerit, Beaumont & Trivin 2011). Fe is considered a highly toxic metal for the liver, where it causes damage leading to micronodular cirrhosis and hepatocellular carcinoma (Pietrangelo 2016). However, recent evidence suggests that iron has weak fibrogenic potential in animals and rarely causes severe human liver damage. It means that Fe is not as significantly hepatotoxic metal as is considered (Bloomer & Brown 2019). We found the highest Fe concentrations in steamed smoked cheese (1.822 mg/kg). Daily reference intake of Fe for adults is recommended at 14 mg (EP 2012). No Tolerable Upper Intake Level has been set for Fe, but the Institute of Medicine has set a daily upper limit (UL) at 45 mg for 14 years and older people, and 40 mg for infants (IOM 2001). The results of our analyses showed that the occurrence of Fe in all products was very low compared to the upper limits. The stated UL values would not be achieved even with higher consumption of the analyzed products. On the other hand, in cheese from Georgia near the contaminated mining area, significantly higher concentrations were found than in our cheeses, reaching values of up to 69.09 and 101.1 mg/kg (Al Sidawi et al. 2021). Depending on the season, Fe concentrations of 0.13 mg/kg (summer) and 0.31 mg/kg (spring) were found in sheep's milk in Slovakia (Toman et al. 2022). In our case, cow's milk from the supermarket contained higher concentrations of Fe. Nevertheless, Pšenková, Toman & Tančin (2020) found the Fe concentration in cow's milk on Slovak farms below the limit of quantification (0.5 mg/kg) regardless of the degree of environmental contamination. Higher values than in our analyzes were found in milk from the market in Slovakia with an average Fe content of 1.76 - 1.92 µg/mL (Capcarova et al. 2019) and in cottage cheese 1.16 - 2.67 µg/g (Capcarova et al. 2020). Concentrations of 0.01 mg/g were found in commercial yogurt analyses in Brazil. At the same time, iron was found in yogurt in the lowest concentration of the monitored elements (Souza et al. 2019). In our work, the values in yogurt were 12 times (producer 2) and 40 times (producer 1) lower. Cow's milk contains low concentrations of Fe and in addition contains a higher concentration of protein and calcium, which negatively affects the absorption of iron from food (Ziegler 2011).

Manganese is known for its neurotoxic effects, although inconsistencies in the assessment of these effects also occur due to differences in exposure duration (Balachandran et al. 2020). This essential metal and its inorganic compounds are considered weak mutagens and carcinogens in vivo (Assem, Holmes & Levy 2011). However, serious findings have been published by Francisco et al. (2021) concerning the mutagenicity of manganese. Concentrations that occurred in ground water had cytotoxic and genotoxic effects in the hamster ovary cells study. With these results, the authors proved that even at concentrations within the permissible limits, Mn can be cytotoxic. DNA damage caused by Mn was detected in human B lymphoblastoid cells. The cytotoxic and genotoxic potential of the monitored metals decreased in the order of Cr>Pb>Cu>Mn (Alimba et al. 2016). Children are particularly sensitive to the toxic effects of Mn. Intake of 133 µg Mn/L reduces their IQ by 1% and at a concentration of 266 µg Mn/L by 2% (Kullar et al. 2019). Mn absorption from breast milk is higher (8.2%) than from cow's

milk (2.4%) (Davidsson et al. 1989). In our analyses of different types of milk, we found the highest concentration of Mn in UHT semi-skimmed milk of producer 1, which was significantly higher than in producer 2. Significantly higher concentrations of Cu were found in the molten cheese of producer 2. However, these values were lower than in other analyzed dairy products. Eidam cheese was again the product that contained the highest concentrations of Mn. Overall, Mn concentrations in our products from the supermarket ranged from 0.007 to 0.284 mg/kg. Higher concentrations of 0.023 - 0.079 mg/L in milk and up to 2.348 mg/kg in Sulguni cheese were found in Georgia (Al Sidawi et al. 2021), 0.092 ppm in milk from the market, 0.130 ppm in the milk of domestic cows in Bangladesh (Muhib et al. 2016), 0.08 - 0.68 µg/g in cottage cheese in Slovakia (Capcarova et al. 2020), 21.05–68.29 µg/L in cow's milk from a supermarket in Turkey (Saribal 2020). The daily reference intake of Mn recommended by Regulation (EU) No. 1169/2011 is 2 mg for adults (EP 2012). Our results show that even the highest concentrations of Mn found in Eidam cheese make up only 1.4% of the recommended daily dose of Mn for adults when consuming 100 g of cheese. We can state that the intake of Mn from milk and dairy products from supermarkets in Slovakia is relatively low.

Nickel is genotoxic and mutagenic, especially at higher doses. This activity is manifested mainly by the formation of DNA-damaging ROS, as well as by the inhibition of DNA repair (Kasprzak, Sunderman & Salnikow 2003). However, nickel hypersensitivity and the development of contact allergic dermatitis are also known (Filatova & Cherpak 2020). There is a risk of children taking this metal during breastfeeding, as it can be found in higher concentrations in breast milk, especially in women who consume water and foods with higher nickel content. For these reasons, regular monitoring of milk for nickel is recommended (Salmani, Mozaffari-Khosravi & Rezaei 2016). In this study, the highest concentration of Ni was found in steamed smoked cheese of producer 1. From the category of milk and dairy drinks, the highest levels of Ni were recorded in whole pasteurized milk of producer 1 and in the category of other dairy products it was in butter of producer 1. Concentrations of Ni in cottage cheese from a supermarket in Slovakia 0.09 - 0.27 µg/g were found by Capcarova et al. (2020). These values are in the range we found in all dairy products from not detected to 0.445 mg/kg. Even lower values than in our case were found in the area of the Mashavera river, which is considered contaminated with heavy metals. Ni was present in cow's milk at concentrations of 0.001 - 0.027 mg/L, in Imeruli cheese at 0.011 mg/kg, and Sulguni cheese at 0.026 mg/kg (Al Sidawi et al. 2021). Psenkova et al. (2020) analyzed cow's milk in different areas of Slovakia. Ni concentrations were below 0.1 mg/kg in areas with an undisturbed environment as well as in areas considered to be severely environmentally disturbed. In other works, similar concentrations were found in the range as in our case: 0.03 mg/200mL in milk in the markets of Sao Luis, Brazil (Ribeiro Sant'Ana, de Carvalho & da Silva 2021), 15 - 40 µg/kg in raw cow's milk in Croatia (Bilandžić et al. 2021), 7.24 - 37.6 µg/L in cow's milk in the various agroclimatic zones of Sri Lanka (Diyabalanage et al. 2021), 38.647 µg/L in cow's milk from a supermarket in Istanbul, Turkey (Saribal 2020). On the other hand, higher Ni concentrations of 0.03 - 1.94 mg/kg in milk and dairy products have been found in Nigeria (Iwegbuel et al. 2013). EFSA established a tolerable daily nickel intake at 13 µg/kg bw (EFSA, 2020). If we are considering consuming 100g of steamed smoked cheese, which we obtained in a supermarket in Slovakia, the intake of Ni is 44.5 µg, which is equal to 0.64 µg for an adult 70 kg person. It means that even the consumption of a dairy product with the highest concentration of Ni that we have found poses no risk for the consumer. Ni intake in this case is approximately 20 times lower than the recommended EFSA limit.

Selenium is an essential element known for its anticarcinogenic effects, but in excess it can be toxic and even mutagenic (Schrauzer 2000; Goldhaber 2003; Kobayashi, Suzuki & Ogra 2018). Various inorganic compounds of Se increase the frequency of chromosomal aberrations on various human cell lines (Valdiglesias et al. 2010). Valdiglesias et al. (2010) further summarize the main food sources of Se based on the literature. Depending on the country, the milk contained Se from 1 - 14 µg/kg (New Zealand) to 19 - 36 µg/kg (Thailand). Se was found in cheeses in quantities ranging from 7.4 - 12 µg/kg (United Kingdom) to 30 - 140 µg/kg (Italy). In our case, we found the highest concentrations of Se 0.293 mg/kg in the category of milk and milk drinks in UHT semi-skimmed milk of producer 1. This means that in our analyses the concentrations of Se in milk were more than 8 times higher than the highest values of Se in milk from Thailand. On the contrary, concentrations below the detection level were found in UHT semi-skimmed milk of producer 2, UHT whole milk and acidophilic white whole milk of

producer 1, as well as in both types of pasteurized milk of both producers. In various contaminated areas in Georgia, Se concentrations were found in milk in the range of 0.005 - 0.042 mg/L, in Imeruli cheese 1.003 mg/kg, and Sulguni cheese 3.06 mg/kg (Al Sidawi et al. 2021), in various areas of Croatia 28 - 52 µg/kg (Bilandžić et al. 2021), in the various agroclimatic zones of Sri Lanka 9.45 - 28.0 µg/L (Diyabalanage et al. 2021), and in cow's milk from a supermarket in Turkey 17.571 µg/L (Saribal 2020). Pšenková, Toman & Tančin (2020) report Se values in cow's milk below 0.03 mg/kg regardless of environmental contamination in northern Slovakia. We found the presence of Se in all types of cheese from both producers with the highest value of 1.75 mg/kg in steamed cheese of producer 2. A significant difference in concentration was recorded between producers in the case of molten cheese of producer 1, where the value of Se was more than 4 times higher than that of producer 2. Significantly higher concentrations were also found in the case of creamy white yogurt of producer 2. Similarly to milk analyzes, we found significantly higher concentrations in cheeses, up to 12.5 times higher than found in Italy (Valdiglesias et al. 2010). However, we found significantly higher values in butter samples (4.102 mg/kg). Daily reference intake of Se recommended by Regulation (EU) No. 1169/2011 is 55 µg for adults (EP 2012). The results show that 1 kg of UHT semi-skimmed milk provides up to 293 µg of Se, which makes up more than 500% of the daily requirement for an adult. The maximum safe level of Se intake in food is considered to be 400 µg (Whanger 2004).

Various metals and other chemical elements manifest their relationships in the human body. Disruption of the balance between the individual elements in the body can lead to a deficiency or excess of an element and consequently to disease (Taylor 1996). However, these relationships also exist in animal products such as milk and dairy products. As milk is contaminated with metals from feed, water, litter, and soil, the interactions between the individual elements are likely related to the environment (Chen et al. 2020). In our correlation analysis, we observed statistically significant relations between several elements. However, correlations between Fe, Cu, and Ni were the most common. Significant positive interactions were found between Fe:Cu in all types of milk except acidophilic white whole milk. In the group of cheeses, these correlations were calculated in steamed cheese, soft lump curd, molten cheese, and other dairy products in all products except cream spread. Sikric et al. (2003) similarly describe relatively strong positive correlations between Cu:Fe ($r = 0.613$) in cow's milk in Croatia. These two metals have similar chemical properties and Cu can affect Fe homeostasis and, conversely, Fe appears to be a Cu antagonist (Doguer, Ha & Collins 2018). However, weak correlations between Cu and Fe were found in raw ewe milk in Slovakia (Toman et al. 2022) and raw milk of Simmental and Holstein-Friesian cows from an organic farm in Poland (Pilarczyk et al. 2013). Contrary to our analyzes, Ribeiro Sant'Ana, de Carvalho & da Silva (2021) found strong negative correlations between Cu and Fe in the UHT milk market in Brazil.

We also recorded frequent correlations between Fe:Ni. Salnikow, Li & Lippmann (2004) report that Fe partially protects cells from the hypoxic effects of nickel, thus exhibiting their antagonistic effects. Positive correlations have been found between Fe and Ni in bone (Kot et al. 2020). In the milk and dairy drinks category, we observed statistically significant strong positive correlations between these elements in all types of milk except whole pasteurized milk and acidophilic white whole milk. Positive correlations were found in UHT milk in Brazil (Ribeiro Sant'Ana, de Carvalho & da Silva 2021). In our previous study, we found strong positive correlations in sheep's milk on a farm in northern Slovakia in the spring (Toman et al. 2022). Positive correlations were also found in the milk of different ruminants (Chen et al. 2020). In contrast, Pšenková, Toman & Tančin (2020) did not record any relationships between Fe and Ni in raw cow's milk in two different areas in Slovakia. Weak negative correlations were found in cow's milk from three producers from a supermarket in Slovakia (Capcarová et al. 2019). In cheeses, strong positive correlations were found between Fe:Ni in Eidam cheese and steamed smoked cheese. Capcarová et al (2020) found both positive and negative correlations of varying degrees in various cottage cheeses from supermarkets in Slovakia. In other dairy products, these elements were in a strong positive correlation in creamy white yogurt and cream spread.

Interactions between Ni and Cu are known. These relationships include Ni and Cu antagonism in various biological systems. Ni intake increased copper levels in the lungs and heart (Spears & Hatfield 1985). Driessnack, Jamwal & Niyogi (2017) report additive toxicity of Ni and Cu on fish reproduction, the interaction of both metals increases their accumulation in specific tissues and causes histopathological

damage in the ovary of fathead minnow (Pimephales promelas). In this study, significant strong positive correlations between Ni:Cu were found in UHT whole milk, UHT semi-skimmed milk and pasteurized semi-skimmed milk. Nevertheless, weak negative correlations were found in raw sheep's milk (Toman et al. 2022). Similarly, weak positive correlations were found in cow's milk from a supermarket in Turkey (Saribal 2020) and Czech UHT milk (Capcarová et al. 2019), and weak negative correlations in the milk of various ruminants (Chen et al. 2020). In cheeses, the two metals were found to have a strong positive correlation in Eidam cheese and steamed smoked cheese. Different relations were found in cottage cheese from a supermarket in Slovakia. In addition to positive correlations, negative correlations were recorded, as well as strong and weak correlations (Capcarova et al. 2020). In other dairy products, significant strong positive correlations were found in creamy white yogurt and whipping cream. However, interactions in different dairy products are lacking in the literature.

In our analyses of milk and dairy products, there were other interactions between many elements, but they were rather rare and often occurred in only 1-2 products and only in one producer. We found a strong positive correlation between Fe:Mn in five cases (UHT semi-skimmed milk, pasteurized semi-skimmed milk, creamy white yogurt, and butter). This relationship was also confirmed in ewe and goat milk by Miedico et al. (2016). Medium to very strong positive correlations were found between Fe:Mn in several types of cottage cheese from a supermarket in Slovakia (lacto-free, chive, tzatziki, mustard-onion, active proteins) (Capcarova et al. 2020). Moderate correlations have also been found in the milk of ruminants in China (Chen et al. 2020), cow's milk in Sri Lanka (Diyabalanage et al. 2021), and cow's milk in Croatia (Sikrić et al. 2003). Iron and manganese are correlated in the body, especially concerning the neurotoxic effects of Mn, which are more pronounced in Fe deficiency (Bjørklund et al. 2020). Frequent interactions were found between various elements and Se. We found the interactions of Se and Pb, Cu, Fe, As, Co, Cr, Mn, and Ni. The antagonistic effects of Se and Cd, As, Cr, Sb, Co in connection with carcinogenic effects are known (Schrauzer 2009). Therefore, it is important to monitor the interrelationships of these elements in the body, but also in food. In our case, significant strong positive correlations were found between Se and As in sheep cheese, sour cream and butter. Positive correlations between Se:As have been found in cow's milk from a supermarket in Turkey. However, these relationships were not statistically significant (Saribal 2020). Weak correlations were found in sheep and goat milk (Miedico et al. 2016), ewe milk during the spring season in Slovakia (Toman et al. 2022), and different milk of ruminants in China (Chen et al. 2020). Zwolak & Zaporowska (2012) reviewed the antagonism of Se and other elements. The authors state that in addition to the mutual interactions between Se and As, Cd, there are also relationships between Se and Cr, V. We found a strong positive correlation between Se:Cr only in molten cheese. On the other hand, weak negative correlations were found in sheep's milk in the uncontaminated area in Slovakia (Toman et al. 2022) and weak positive correlations were found in ruminant milk in China (Chen et al. 2020). Metabolic interactions have been observed between Se and Cu (Mudgal et al. 2018). In this work, we observed strong positive correlations between Se:Cu in molten cheese, soft lump curd, and butter. Positive correlations between the two elements have also been found in breast milk in Finland (Kantol & Vartiainen 2001) and in Italy (Perrone et al. 1994), so the observed relations between Se and other metals in milk is probably due to the effect of Se intake in animal feed and food of mothers. Interactions of Cr and Pb were found in Taiwanese adult population with kidney function damage (Tsai et al. 2017). However, interactions between the two metals also exist in animal products such as milk and dairy products. In our work, we have noted their strong positive correlations in steamed smoked cheese, molten cheese, sheep cheese, and sour cream. Chen et al. (2020) found similar trends in ruminant milk. On the other hand, a strong negative correlation was found in chili cottage cheese from Slovak supermarket (Capcarova et al. 2020), as well as weak correlations in raw milk of sheep in Slovakia (Toman et al. 2022). More significant interactions were found between different elements in this work. However, they were not as frequent as in previous relationships. Nevertheless, it is important to mention the interactions of As with the essential elements that we have found in the individual products. Arsenic is a toxic element characterized by mutagenic and carcinogenic effects and its effect on essential elements can have a negative impact on health and, in the case of food, on the nutritional value of food. In our analyzed products, there were correlations between As and Fe, Co, Cr, Cu, Mn, Ni, but also Pb. In ruminant milk, strong positive correlations were

found between As:Cr (Chen et al. 2020), which is consistent with our results in Eidam cheese. In contrast to these results, strong negative correlations were found in raw sheep's milk (Toman et al. 2022).

5. CONCLUSIONS

The presence of mutagenic elements in milk and dairy products in the retail network is a serious problem in terms of consumer health. The result of our analysis is the finding that some elements were present in concentrations that could be hazardous due to the nature of the metals. These were mainly higher values of As, especially in butter, Cr concentrations at the level of TDI in molten cheese, and Pb values in UHT whole milk exceeding the limit. Other elements do not pose any risk with the regular intake of these products. In the case of Co, Cu, Fe, and Mn, these metals were rather present at low concentrations. On the contrary, we recorded relatively high concentrations of selenium in UHT semi-skimmed milk. The consumption of this milk covers up to 500% of the daily requirement for an adult. The findings of several significant strong correlations between the elements are also important. The most common correlations were calculated between Fe, Cu, and Ni. As milk and dairy products are among the basic foods consumed by the most vulnerable groups of people, namely children and the elderly, it is essential to monitor their presence in milk and dairy products.

ACKNOWLEDGMENTS

This work was supported by the Slovak Research and Development Agency under the Contract no. APVV-18-0227.

REFERENCES

1. Abrahim, KS, Abdel-Gawad, NB, Mahmoud, AM, El-Gowaily, MM, Emara, AM & Hwaihy, MM 2011, “Genotoxic effect of occupational exposure to cadmium”, *Toxicology and Industrial Health*, vol. 27, no. 2, pp. 173-179.
2. Adeyemi, JA, Machado, ART, Ogunjimi, AT, Alberici, LC, Antunes, LMG & Barbosa, F Jr 2020, “Cytotoxicity, mutagenicity, oxidative stress and mitochondrial impairment in human hepatoma (HepG2) cells exposed to copper oxide, copper-iron oxide and carbon nanoparticles”, *Ecotoxicology and Environmental Safety*, vol. 189, pp. 109982.
3. Alimba, CG, Dhillon, V, Bakare, AA & Fenech, M 2016, “Genotoxicity and cytotoxicity of chromium, copper, manganese and lead, and their mixture in WIL2-NS human B lymphoblastoid cells is enhanced by folate depletion”, *Mutation Research*/Genetic *Toxicology and Environmental Mutagenesis*, vol. 798-799, pp. 35-47.
4. Al Sidawi, R, Ghambashidze, G, Urushadze, T & Ploeger A 2021, “Heavy metal levels in milk and cheese produced in the Kvemo Kartli region, Georgia”, *Foods*, vol. 10, no. 9, pp. 2234.
5. Assem, FL, Holmes, P & Levy, LS 2011, “The mutagenicity and carcinogenicity of inorganic manganese compounds: a synthesis of the evidence”, *Journal of Toxicology and Environmental Health B*, vol. 14, no. 8, pp. 537–570.
6. Balachandran, RC, Mukhopadhyay, S, McBride, D, Veevers, J, Harrison, FE, Aschner, M, Haynes, EN & Bowman, AB 2020, “Brain manganese and the balance between essential roles and neurotoxicity”, *Journal of Biological Chemistry*, vol. 295, no. 19, pp. 6312-6329.
7. Barbier, O, Jacquillet, G, Tauc, M, Cougnon, M & Poujeol, P 2005, “Effect of heavy metals on, and handling by, the kidney”, *Nephron Physiology*, vol. 99, no. 4, pp. 105-110.

8. Batschauer, AR, Souza, TL, Manuitt, Brito, PE, Neto, FF, Oliveira Ribeiro, CA & Ortolani-Machado, CF 2021, "Behavioral and neurochemical effects in mice after one-generation exposure to low doses of manganese: Focus on offspring development", *Chemico-Biological Interactions*, vol. 345, pp. 109532.
9. Bilandžić, N, Čalopek, B, Sedak, M, Đokić, M, Tlak Gajger, I, Muratic, T & Kmetič, I 2021, "Essential and potentially toxic elements in raw milk from different geographical regions of Croatia and their health risk assessment in the adult population", *Journal of Food Composition and Analysis*, vol. 104, pp. 104152.
10. Briffa, J, Sinagra, E & Blundell, R 2020, "Heavy metal pollution in the environment and their toxicological effects on humans", *Heliyon*, vol. 6, no. 9, pp. 04691.
11. Bjørklund, G, Dadar, M, Peana, M, Rahaman, MS & Aaseth, J 2020, "Interactions between iron and manganese in neurotoxicity", *Archives of Toxicology*, vol. 94, no. 3, pp. 725-734.
12. Bloomer, SA & Brown, KE 2019, "Iron-induced liver injury: A critical reappraisal", *International Journal of Molecular Sciences*, vol. 20, no. 9, pp. 2132.
13. Brown, S, Lockart, MM, Thomas, CS, Bowman, MK, Woski, SA & Vincent, JB 2020, "Molecular structure of binary chromium(III)-DNA adducts", *ChemBioChem*, vol. 21, no. 5, pp. 628-631.
14. Campanella, B, Colombaioni, L, Benedetti, E, Di Ciaula, A, Ghezzi, L, Onor, M, D'Orazio, M, Giannecchini, R, Petrini, R & Bramanti, E 2019, "Toxicity of thallium at low doses: A review. *International Journal of Environmental Research and Public Health*, vol. 16, no. 23, pp. 4732.
15. Capcarova, M, Binkowski, LJ, Stawarz, R, Schwarczova, L & Massanyi, P 2019, "Levels of essential and xenobiotic elements and their relationships in milk available on the Slovak market with the estimation of consumer exposure. *Biological Trace Element Research*, vol. 188, no. 2, pp. 404-411.
16. Capcarova, M, Harangozo, L, Arvay, J, Toth, T, Gabriny, L, Binkowski, LJ, Palsova, L, Skalicka, M, Pardo, MLG, Stawarz, R & Massanyi, P 2020, "Essential and xenobiotic elements in cottage cheese from the Slovak market with a consumer risk assessment", *Journal Environmental Science and Health B*, vol. 55, no. 7, pp. 677-686.
17. Chen, L, Li, X, Li, Z & Deng, L 2020, "Analysis of 17 elements in cow, goat, buffalo, yak, and camel milk by inductively coupled plasma mass spectrometry (ICP-MS)". *RSC Advances*, vol. 10, no. 12, pp. 6736-6742.
18. Chen, X, Xu, Y, Cheng, Z, Su, H, Liu, X, Xu, D, Kapron, C & Liu, J 2018, "Low-dose cadmium activates the JNK signaling pathway in human renal podocytes", *International Journal of Molecular Medicine*, vol. 41, no. 4, pp. 2359-2365.
19. Cobbina, SJ, Chen, Y, Zhou, Z, Wu, X, Feng, W, Wang, W, Li, Q, Zhao, T, Mao, G, Wu, X & Yang, L 2015a, "Interaction of four low dose toxic metals with essential metals in brain, liver and kidneys of mice on sub-chronic exposure", *Environmental Toxicology and Pharmacology*, vol. 39, No. 1, pp. 280-291.
20. Cobbina, SJ, Chen, Y, Zhou, Z, Wu, X, Zhao, T, Zhang, Z, Feng, W, Wang, W, Li, Q, Wu, X & Yang, L 2015b, "Toxicity assessment due to sub-chronic exposure to individual and mixtures of four toxic heavy metals", *Journal of Hazardous Materials*, vol. 294, pp. 109-120.
21. Cobbina, SJ, Chen, Y, Zhou, Z, Wu, X, Feng, W, Wang, W, Mao, G, Xu, H, Zhang, Z, Wu, X & Yang, L 2015c, "Low concentration toxic metal mixture interactions: Effects on essential and non-essential metals in brain, liver, and kidneys of mice on sub-chronic exposure", *Chemosphere*, vol. 132, pp. 79-86.

22. Čėsnienė, T, Kleizaitė, V, Bondzinskaitė, S, Taraškevičius, R, Žvingila, D, Šiukšta, R & Rančelis V 2017, "Metal bioaccumulation and mutagenesis in a Tradescantia clone following long-term exposure to soils from urban industrial areas and closed landfills", *Mutation Research*/Genetic *Toxicology and Environmental Mutagenesis*, vol. 823, pp. 65-72.
23. Davidsson, L, Cederblad, A, Lönnerdal, B & Sandström, B 1989, "Manganese absorption from human milk, cow's milk, and infant formulas in humans", *American Journal of Diseases of Children*, vol. 143, no. 7, pp. 823-827.
24. Diyabalanage, S, Kalpage, MD, Mohotti, DG, Dissanayake, CKK, Fernando, R, Frew, RD & Chandrajith, R 2021, "Comprehensive assessment of essential and potentially toxic trace elements in bovine milk and their feeds in different agro-climatic zones of Sri Lanka. *Biological Trace Element Research*, vol. 199, no. 4, pp. 1377-1388.
25. Doguer, C, Ha, JH & Collins, JF 2018, "Intersection of iron and copper metabolism in the mammalian intestine and liver", *Comprehensive Physiology*, vol. 8, no. 4, pp. 1433-1461.
26. Duranova, H, Martiniakova, M, Omelka, R, Grosskopf, B, Bobonova, I & Toman R 2014, "Changes in compact bone microstructure of rats subchronically exposed to cadmium", *Acta Veterinaria Scandinavica*, vol. 56, no. 1, pp. 64.
27. Eastmond, DA, Hartwig, A, Anderson, D, Anwar, WA, Cimino, MC, Dobrev, I, Douglas, GR, Nohmi, T, Phillips, DH & Vickers, C 2009, "Mutagenicity testing for chemical risk assessment: update of the WHO/IPCS Harmonized Scheme", *Mutagenesis*, vol. 24, pp. 341-349.
28. EC 2021, "Commission Regulation (EU) 2021/1317 of 9 August 2021 amending Regulation (EC) No 1881/2006 as regards maximum levels of lead in certain foodstuffs", *Official Journal of the European Union*, vol. 64, pp. 1-4.
29. EFSA 2014, "Dietary exposure to inorganic arsenic in the European population", *EFSA Journal*, vol. 12, no. 3, pp. 3597.
30. EFSA 2020, "Update of the risk assessment of nickel in food and drinking water", *EFSA Journal*, vol. 18, no. 11, pp. 6268.
31. EFSA CONTAM Panel 2009, "Scientific opinion on arsenic in food", *EFSA Journal*, vol. 7, no. 10, pp. 1351.
32. EFSA CONTAM Panel 2014, "Scientific opinion on the risks to public health related to the presence of chromium in food and drinking water", *EFSA Journal*, vol. 12, no. 3, pp. 3593.
33. Emerit, J, Beaumont, C & Trivin, F 2001, "Iron metabolism, free radicals, and oxidative injury", *Biomedicine & Pharmacotherapy*, vol. 55, no. 6, pp. 333-339.
34. EP 2012, "Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004", *Official Journal of the European Union*, L304, pp. 18-63.
35. Fan, G, Zhou, F & Feng, C 2017, "Toxic effects of combined exposure to four heavy metals at low doses", *Journal of Hazardous Materials*, vol. 323, Pt B, pp. 737-738.
36. FEEDAP 2012, "Scientific opinion on safety and efficacy of cobalt carbonate as feed additive for ruminants, horses and rabbits", *EFSA Journal*, vol. 10, no. 6, pp. 2727.
37. Fernandes Azevedo, B, Barros Furieri, L, Peçanha, FM, Wiggers, GA, Frizera Vassallo, P, Ronacher Simões, M, Fiorim, J, Rossi de Batista, P, Fioresi, M, Rossoni, L, Stefanon, I, Alonso, MJ, Salaices, M & Valentim Vassallo, D 2012, "Toxic effects of mercury on the cardiovascular and central nervous systems", *Journal of Biomedicine and Biotechnology*, vol. 2012, pp. 949048.

38. Filatova, D & Cherpak, C 2020, "Mechanisms of nickel-induced cell damage in allergic contact dermatitis and nutritional intervention strategies", *Endocrine*, *Metabolic & Immune Disorders - Drug Targets*, vol. 20, no. 7, pp. 1010-1014.
39. Francisco, LFV, Baldivia, DDS, Crispim, BDA, Klafke, SMFF, Castilho, PF, Viana, LF, Santos, ELD, Oliveira, KMP & Barufatti, A 2021, "Acute toxic and genotoxic effects of aluminum and manganese using in vitro models", *Toxics*, vol. 9, no. 7, pp. 153.
40. Gaucheron, F 2005, "The minerals of milk", *Reproduction Nutrition Development,* vol. 45, pp. 473-483.
41. Gaucheron, F 2011, "Milk and dairy products: a unique micronutrient combination", *Journal of the American College of Nutrition*, vol. 30, no. 5, Suppl 1, pp. 400S-409S.
42. Gidlow, DA 2015, "Lead toxicity", *Occupational Medicine (London)*, vol. 65, no. 5, pp. 348-356.
43. Goldhaber, SB 2003, "Trace element risk assessment: essentiality vs. toxicity", *Regulatory Toxicology and Pharmacology*, vol. 38, no. 2, pp. 232-242.
44. Haney, J Jr 2015, "Use of dose-dependent absorption into target tissues to more accurately predict cancer risk at low oral doses of hexavalent chromium", *Regulatory Toxicology and Pharmacology*, vol. 71, no. 1, pp. 93-100.
45. Hartwig, A, Asmuss, M, Ehleben, I, Herzer, U, Kostelac, D, Pelzer, A, Schwerdtle, T & Bürkle, A 2002, "Interference by toxic metal ions with DNA repair processes and cell cycle control: molecular mechanisms", *Environmental Health Perspectives*, vol. 110, pp. 797-799.
46. Hemmaphan, S & Bordeerat, NK 2022, "Genotoxic effects of lead and their impact on the expression of DNA repair genes", *International Journal of Environmental Research and Public Health*, vol. 19, no. 7, pp. 4307.
47. Ibrahem, S, Hassan, M, Ibraheem, Q & Arif, K 2020, "Genotoxic effect of lead and cadmium on workers at wastewater plant in Iraq", *Journal of Environmental and Public Health*, vol. 2020, pp. 9171027.
48. Iwegbuel, CM, Ossai, EK, Overah, CL & Nwajei, GE 2013, "Trace metal contents in some milk and milk products in Nigeria", *Journal of Environmental Science and Engineering*, vol. 55, no. 1, pp. 101-107.
49. IOM 2001, "*Iron*", In *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*". Washington (DC): National Academies Press (US), p. 290-393.
50. Jadhav, SH, Sarkar, SN & Tripathit, HC 2006, "Cytogenetic effects of a mixture of selected metals following subchronic exposure through drinking water in male rats", *Indian Journal of Experimental Biology*, vol. 44, no. 12, pp. 997-1005.
51. Javorac, D, Antonijević, B, Anđelković, M, Repić, A, Bulat, P, Djordjevic, AB, Baralić, K, Đukić-Ćosić, D, Antonić, T & Bulat Z 2021, "Oxidative stress, metallomics and blood toxicity after subacute low-level lead exposure in Wistar rats: Benchmark dose analyses", *Environmental Pollution*, vol. 291, pp. 118103.
52. Javorac, D, Tatović, S, Anđelković, M, Repić, A, Baralić, K, Djordjevic, AB, Mihajlović, M, Stevuljević, JK, Đukić-Ćosić, D, Ćurčić, M, Antonijević, B & Bulat, Z 2022, "Low-lead doses induce oxidative damage in cardiac tissue: Subacute toxicity study in Wistar rats and Benchmark dose modelling", *Food and Chemical Toxicology*, vol. 161, pp. 112825.
53. Jha, AN, Noditi, M, Nilsson, R & Natarajan, AT 1992, "Genotoxic effects of sodium arsenite on human cells", *Mutation Research*, vol. 284, no. 2, pp. 215-221.
54. Jomova, K & Valko, M 2011, "Advances in metal-induced oxidative stress and human disease", *Toxicology*, vol. 283, no. 2-3, pp. 65-87.

55. Kantol, M & Vartiainen T 2001, "Changes in selenium, zinc, copper and cadmium contents in human milk during the time when selenium has been supplemented to fertilizers in Finland", *Journal of Trace Elements in Medicine and Biology*, vol. 15, no. 1, pp. 11-17.
56. Kasprzak, KS, Sunderman, FW Jr & Salnikow, K 2003, "Nickel carcinogenesis", *Mutation Research*, vol. 533, no. 1-2, pp. 67-97.
57. Kincaid, RL & Socha, MT 2007, "Effect of cobalt supplementation during late gestation and early lactation on milk and serum measures", *Journal of Dairy Science*, vol. 90, no. 4, pp. 1880-1886.
58. Kinney, DK, Barch, DH, Chayka, B, Napoleon, S & Munir, KM 2010, "Environmental risk factors for autism: do they help cause de novo genetic mutations that contribute to the disorder?" *Medical hypotheses*, vol. 74, no. 1, pp. 102–106.
59. Kobayashi, H, Suzuki, N & Ogra, Y 2018, "Mutagenicity comparison of nine bioselenocompounds in three Salmonella typhimurium strains", *Toxicology Reports*, vol. 5, pp. 220-223.
60. Kocadal, K, Alkas, FB, Ulutas, OK, Kurt, MA, Battal, D, Sardas, S, Etikan, I & Saygi, S 2021, "Biomonitoring of heavy metal(oid)s in the residents of abandoned mining district in Northern Cyprus", *Biological Trace Element Research*, vol. 199, no. 10, pp. 3667-3676.
61. Koedrith, P, Kim, H, Weon, JI & Seo, YR 2013, "Toxicogenomic approaches for understanding molecular mechanisms of heavy metal mutagenicity and carcinogenicity", *International Journal of Hygiene and Environmental Health,* vol. 216, no. 5, pp. 587-598.
62. Kot, K, Kosik-Bogacka, D, Ziętek, P, Karaczun, M, Ciosek, Ż & Łanocha-Arendarczyk, N 2020, "Impact of varied factors on iron, nickel, molybdenum and vanadium concentrations in the knee joint", *International Journal of Environmental Research and Public Health*, vol. 17, no. 3, pp. 813.
63. Kullar, SS, Shao, K, Surette, C, Foucher, D, Mergler, D, Cormier, P, Bellinger, DC, Barbeau, B, Sauvé, S & Bouchard, MF 2019, "A benchmark concentration analysis for manganese in drinking water and IQ deficits in children", *Environment International*, vol. 130, pp. 104889.
64. Kumar, C, Rana, RK, Kumar, M, Kujur, A, Kashyap, V, Singh, SB, Sagar, V, Kumari, N & Kumar, D 2021, "Effect of milk supplementation on the status of micronutrients among rural school children aged 5-19 years in a tribal predominating district of India", *BMJ Nutrition*, *Prevention & Health*, vol. 4, no. 2, pp. 463-468.
65. Kumar, S & Sharma, A 2019, "Cadmium toxicity: effects on human reproduction and fertility", *Reviews on Environmental Health*, vol. 34, no. 4, pp. 327-338.
66. Kuriyan, R, Thankachan, P, Selvam, S, Pauline, M, Srinivasan, K, Kamath-Jha, S, Vinoy, S, Misra, S, Finnegan, Y & Kurpad AV 2016, "The effects of regular consumption of a multiple micronutrient fortified milk beverage on the micronutrient status of school children and on their mental and physical performance", *Clinical Nutrition*, vol. 35, no. 1, pp. 190-198.
67. Leelapongwattana, S & Bordeerat, NK 2020, "Induction of genotoxicity and mutagenic potential of heavy metals in Thai occupational workers", *Mutation Research*/Genetic *Toxicology and Environmental Mutagenesis*, vol. 856-857, pp. 503231.
68. Lison, D, van den Brule, S & Van Maele-Fabry, G 2018, "Cobalt and its compounds: update on genotoxic and carcinogenic activities", *Critical Reviews in Toxicology*, vol. 48, no. 7, pp. 522-539.
69. Maas, S, Lucot, E, Gimbert, F, Crini, N & Badot, PM 2011, "Trace metals in raw cows' milk and assessment of transfer to Comté cheese", *Food Chemistry*, vol. 129, no. 1, pp. 7-12.
70. Meshref, AMS, Moselhy, WA & Hassan, NEHY 2014, "Heavy metals and trace elements levels in milk and milk products", *Food Measure*, vol. 8, pp. 381–388.
71. Miedico, O, Tarallo, M, Pompa, C & Chiaravalle, AE 2016, "Trace elements in sheep and goat milk samples from Apulia and Basilicata regions (Italy): valuation by multivariate data analysis", *Small Ruminant Research*, vol. 135, pp. 60–65.

72. Mohamed, HRH 2021, "Alleviation of cadmium chloride-induced acute genotoxicity, mitochondrial DNA disruption, and ROS generation by chocolate coadministration in mice liver and kidney tissues. *Biological Trace Element Research*, doi: 10.1007/s12011-021-02981-y.

73. Mudgal, V, Garg, AK, Dass, RS & Rawat, M 2018, "Selenium and copper interaction at supra-nutritional level affecting blood parameters including immune response against P. multocida antigen in Murrah buffalo (Bubalus bubalis) calves", *Journal of Trace Elements in Medicine and Biology*, vol. 50, pp. 415-423.

74. Muhib, MI, Chowdhury, MAZ, Easha, NJ, Rahman, MdM, Shammi, M, Fardous, Z, Bari, ML, Uddin, MK, Kurasaki, M & Alam, MK 2016, "Investigation of heavy metal contents in Cow milk samples from area of Dhaka, Bangladesh", *International Journal of Food Contamination*, vol. 3, pp. 16.

75. Onakpa, MM, Njan, AA & Kalu, OC 2018, "A review of heavy metal contamination of food crops in Nigeria", *Annals of Global Health*, vol. 84, no. 3, pp. 488-494.

76. O'Neill, NC & Tanner, MS 1989, "Uptake of copper from brass vessels by bovine milk and its relevance to Indian childhood cirrhosis", *Journal* of *Pediatric Gastroenterology and Nutrition*, vol. 9, no. 2, pp. 167-172.

77. Page, K, Harbottle, MJ, Cleall, PJ & Hutchings, TR 2014, "Heavy metal leaching and environmental risk from the use of compost-like output as an energy crop growth substrate", *Science of the Total Environment*, vol. 487, pp. 260-271.

78. Pal, A 2014, "Copper toxicity induced hepatocerebral and neurodegenerative diseases: an urgent need for prognostic biomarkers", *Neurotoxicology*, vol. 40, pp. 97-101.

79. Perrone, L, Di Palma, L, Di Toro, R, Gialanella, G & Moro, R 1994, "Interaction of trace elements in a longitudinal study of human milk from full-term and preterm mothers", *Biological Trace Element Research*, vol. 41, no. 3, pp. 321-330.

80. Pietrangelo, A 2016, "Mechanisms of iron hepatotoxicity", *Journal of Hepatology*, vol. 65, no. 1, pp. 226-227.

81. Pilarczyk, R, Wójcik, J, Czerniak, P, Sablik, P, Pilarczyk, B & Tomza-Marciniak, A 2013, "Concentrations of toxic heavy metals and trace elements in raw milk of Simmental and Holstein-Friesian cows from organic farm", *Environmental Monitoring and Assessment*, vol. 185, no. 10, pp. 8383-8392.

82. Pipoyan, D, Hovhannisyan, A, Beglaryan, M & Mantovani, A 2022, "Risk assessment of potentially toxic trace elements via consumption of dairy products sold in the city of Yerevan, Armenia". *Food and Chemical Toxicology*, vol. 163, pp. 112922.

83. Prá, D, Franke, SI, Giulian, R, Yoneama, ML, Dias, JF, Erdtmann, B & Henriques, JA 2008, "Genotoxicity and mutagenicity of iron and copper in mice", *Biometals*, vol. 21, no. 3, pp. 289-297.

84. Pšenková, M, Toman, R & Tančin, V 2020, "Concentrations of toxic metals and essential elements in raw cow milk from areas with potentially undisturbed and highly disturbed environment in Slovakia", *Environmental Science and Pollution Research*, vol. 27, no. 21, pp. 26763-26772.

85. Rădulescu, A & Lundgren, S 2019, "A pharmacokinetic model of lead absorption and calcium competitive dynamics", *Scientific Reports*, vol. 9, no. 1, pp. 14225.

86. Reutova, NV 2017, "Mutagenic potential of some heavy metals" *Russian Journal of Genetics*: *Applied Research*, vol. 7, pp. 175–179.

87. Ribeiro Sant'Ana, MA, de Carvalho, TC & da Silva, IF 2021, "Concentration of heavy metals in UHT dairy milk available in the markets of São Luís, Brazil, and potential health risk to children", *Food Chemistry*, vol. 346, pp. 128961.

88. Roychoudhury, S, Massanyi, P, Bulla, J, Choudhury, MD, Lukac, N, Filipejova, T, Trandzik, J, Toman, R & Almasiova, V 2010, "Cadmium toxicity at low concentration on rabbit spermatozoa motility, morphology and membrane integrity in vitro", *Journal of Environmental Science and Health A*, vol. 45, no. 11, pp. 1374-1383.

89. Salmani, MH, Mozaffari-Khosravi, H & Rezaei, Z 2016, "The nickel concentration in breast milk during the first month of lactation in Yazd, center of Iran", *Biological Trace Element Research*, vol. 174, no. 1, pp. 65-70.

90. Sarsembayeva, NB, Abdigaliyeva, TB, Utepova, ZA, Biltebay, AN & Zhumagulova, SZ 2019, "Heavy metal levels in milk and fermented milk products produced in the Almaty region, Kazakhstan", *Veterinary World*, vol. 13, no. 4, pp. 609–613.

91. Saribal D 2020, "ICP-MS analysis of trace element concentrations in cow's milk samples from supermarkets in Istanbul, Turkey", *Biological Trace Element Research*, vol. 193, no. 1, pp.166-173.

92. Schrauzer GN 2000, "Anticarcinogenic effects of selenium", *Cellular and Molecular Life Sciences*, vol. 57, no. 13-14, pp. 1864-1873.

93. Schrauzer GN 2009, "Selenium and selenium-antagonistic elements in nutritional cancer prevention", *Critical Reviews in Biotechnology*, vol. 29, no. 1, pp. 10-17.

94. Sikrić, M, Brajenović, N, Pavlović, I, Havranek, JL & Plavljanić, N 2003, "Determination of metals in cow's milk by flame atomic absorption spectrophotometry. *Czech Journal of Animal Science*, vol. 48, no. 11, pp. 481–486.

95. Simonsen, LO, Harbak, H & Bennekou, P 2012, "Cobalt metabolism and toxicology-a brief update", *Science of the Total Environment*, vol. 432, pp. 210-215.

96. Sobhanardakani, S 2018, "Human health risk assessment of Cd, Cu, Pb and Zn through consumption of raw and pasteurized cow's milk", *Iranian Journal of Public Health*, vol. 47, no. 8, pp. 1172–1180.

97. Souza, TSP, Luna, AS, Barros, DB, Pimentel, TC, Pereira, EPR, Guimarães, JT, Esmerino, EA, Freitas, MQ, Costa, RGB, Silva, MC, Quitério, SL, Raices, RSL & Cruz, AG 2019, "Yogurt and whey beverages available in Brazilian market: Mineral and trace contents, daily intake and statistical differentiation", *Food Research International*, vol. 119, pp. 709-714.

98. Spears, JW & Hatfield, EE 1985, "Interaction between nickel and copper in the rat", *Biological Trace Element Research*, vol. 7, no. 3, pp. 181-193.

99. Sun, HJ, Rathinasabapathi, B, Wu, B, Luo, J, Pu, LP & Ma, LQ 2014, "Arsenic and selenium toxicity and their interactive effects in humans". *Environment International*, vol. 69, pp. 148-158.

100. Taylor, A 1996, "Detection and monitoring of disorders of essential trace elements", *Annals of Clinical Biochemistry*, vol. 33, no. 6, pp. 486-510.

101. Toman, R, Psenkova, M, Tancin, V & Miskeje, M 2022, "Mutagens in raw ewe milk in Orava region, northern Slovakia: metals", *Environmental Science and Pollution Research*, doi: 10.1007/s11356-022-20871-1.

102. Tripathi, RM, Raghunath, R, Sastry, VN & Krishnamoorthy, TM 1999, "Daily intake of heavy metals by infants through milk and milk products", Science of the Total Environment, vol. 227, no. 2-3, pp. 229-235.

103. Tsai, TL, Kuo, CC, Pan, WH, Chung, YT, Chen, CY, Wu, TN & Wang, SL 2017, "The decline in kidney function with chromium exposure is exacerbated with co-exposure to lead and cadmium", *Kidney International*, vol. 92, no. 3, pp. 710-720.

104. Tunegová, M, Samková, E, Hasoňová, L, Klimešová, M, Marková, A, Kala, R & Toman, R 2018, "Occurrence of chemical contaminants in animal products during 1999–2016 in the Czech Republic", *British Food Journal*, vol. 120, no. 9, pp. 2142-2154.

105. Valdiglesias, V, Pásaro, E, Méndez, J & Laffon, B 2010, "In vitro evaluation of selenium genotoxic, cytotoxic, and protective effects: a review", *Archives* of *Toxicology*, vol. 84, no. 5, pp. 337-351.

106. Vassallo, DV, Wiggers, GA, Padilha, AS & Simões, MR 2020, "Endothelium: A target for harmful actions of metals", *Current Hypertension Reviews*, vol. 16, no. 3, pp. 201-209.

107. Whanger, PD 2004, "Selenium and its relationship to cancer: an update", *British Journal of Nutrition*, vol. 91, no. 1, pp. 11–28.

108. Wise, JP Sr, Wise, SS & Little, JE 2002, "The cytotoxicity and genotoxicity of particulate and soluble hexavalent chromium in human lung cells", *Mutation Research*, vol. 517, no. 1-2, pp. :221-229.

109. Wu, X, Cobbina, SJ, Mao, G, Xu, H, Zhang, Z & Yang, L 2016, "A review of toxicity and mechanisms of individual and mixtures of heavy metals in the environment", *Environmental Science and Pollution Research*, vol. 23, no. 9, pp. 8244-8259.

110. Zhang, N, Yang, S, Yang, J, Deng, Y, Li, S, Li, N, Chen, X, Yu, P, Liu, Z & Zhu, J 2020, "Association between metal cobalt exposure and the risk of congenital heart defect occurrence in offspring: a multi-hospital case-control study", *Environmental Health and Preventive Medicine,* vol. 25, no. 1, pp. 38.

111. Zhou, Q & Xi, S 2018, "A review on arsenic carcinogenesis: Epidemiology, metabolism, genotoxicity and epigenetic changes", *Regulatory Toxicology and Pharmacology*, vol. 99, pp. 78-88.

112. Ziegler, EE 2011, "Consumption of cow's milk as a cause of iron deficiency in infants and toddlers". *Nutrition Reviews*, vol. 69, Suppl 1, pp. S37-42.

113. Zwolak, I & Zaporowska, H 2012, "Selenium interactions and toxicity: a review. Selenium interactions and toxicity", *Cell Biology and Toxicology*, vol. 28, no. 1, pp. 31-46.