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The levels, single and multiple health risk assessment of 23 metals in enteral nutrition formulas

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ABSTRACT

Enteral nutrition formulas are products that provide macro and micronutrients to patients who cannot receive their nutrition orally. In this study, the levels of 23 metals known to have potential health risks were determined by inductively coupled plasma mass spectrometry in a total of 28 enteral nutrition formula. Metal exposure was calculated according to three different daily energy intake scenarios (Scenario 1 = 50% oral nutrition + 50% enteral nutrition formula, Scenario 2 = 25% oral nutrition + 75% enteral nutrition formula and Scenario 3 = 100% enteral nutrition formula) and evaluated in terms of non-carcinogenic health risks. The mean levels of Fe, Co, Ni, Cu, Zn, Mo, Se, Li, Be, V, As, Sr, Ag, Cd, Sb, Ba, La, Hg and Pb in the samples analyzed were determined 12,000 ± 3300, 64 ± 1.6, 10 ± 13, 1300 ± 400, 8500 ± 2500, 75 ± 30, 61 ± 21, 0.34 ± 0.36, 0.05 ± 0.08, 7.3 ± 2, 1.6 ± 0.6, 457 ± 166, 0.02 ± 0.1, 0.14 ± 0.12, 0.01 ± 0.1, 74 ± 103, 0.63 ± 0.4, 0.05 ± 0.03 and 0.14 ± 0.7 μg/L. These metals were considered safe in terms of non-carcinogenic health risks when analyzed individually. However, when the target hazard quotient values of all metals were evaluated together, hazard index values were higher than the reference value of 1, for both men and women, indicating potential health risks.

1. Introduction

Enteral nutrition formulas (ENFs) are specialised products that are administered directly into the stomach or intestine of patients who are unable to meet their daily nutritional and energy needs with a regular diet, either by oral intake or using a tube or catheter (Iturbide-Casas et al., 2019). Most of the ENFs offered for sale in the market are in liquid form, and there are ENFs developed for many different purposes, such as standard (polymeric), disease-specific, and specialty formulations with phytonutrients (Brown et al., 2015). The patient's clinical condition determines the use of ENFs, the treatment is administered, and the individual needs or age of the patient, and all of these processes are carried out under the supervision of a specialist (Church and Zoeller, 2023). ENFs are enriched with many different macro- and micronutrients to provide humans with the essential nutrients and energy required (Cámara-Martos and Iturbide-Casas, 2019). However, since the US Food and Drug Administration does not recognise medical foods as drugs, there is no regulatory requirement to determine the safety and clinical effects of ENFs before production and marketing (Food and Drug Administration, 2023). However, it should be noted that ENFs, like many other food products, may contain some metals that pose potential risks to human health, considering both the raw and auxiliary materials used in the product formulation and the process conditions.

Metals pollute the environment through natural phenomena, such as erosion of rocks, volcanic eruptions and man-made activities, such as industrial activities, urbanization, motor vehicle use and wastes (Garrett, 2000; Rodríguez-Espinosa et al., 2018; Vareda et al., 2019). The transfer of metals to human metabolism occurs through inhalation, ingestion and skin (Fu and Xi, 2020). Metals are bioaccumulative and are challenging to metabolize after being taken into the body (Liu et al., 2019). Although some metals, such as cobalt (Co), iron (Fe), selenium (Se), zinc (Zn), chromium (Cr), manganese (Mn) and copper (Cu), are essential elements for various biochemical and physiological functions in humans, it has also been reported that these metals may cause various diseases due to their accumulation properties (Zoroddu et al., 2019; Jomova et al., 2022). On the other hand, metals, such as cadmium (Cd), arsenic (As), mercury (Hg) and lead (Pb), are heavy metals that are not essential for all living organisms. Accumulation of metals has been associated with mutagenic, teratogenic and carcinogenic toxicity in many systems, such as gastrointestinal, cardiovascular and neurological (Fu and Xi, 2020; Dasharathy et al., 2022; Priyadarshanee et al., 2022; Michalczyk et al., 2023).

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Table 1
Analysis of the recovery, LOD, LOQ and calibration (R^2) for the heavy metals.

Elements	Concentration (μg/L)	Mean Recovery (%)	Linear equation x, y (μg/L)	R^2	LOD (μg/L)	LOQ (μg/L)
Li	0, 10, 25, 50,100, 250, 500	112	y = 0.0038*x+0.0061	0.9991	0.397	1.323
Be	0, 10, 25, 50,100, 250, 500	89	y = 0.0030*x+1.1441E-004	0.9991	0.067	0.224
V	0, 10, 25, 50,100, 250, 500	111	y = 0.1367*x+0.0157	0.9992	0.003	0.010
Cr	0, 10, 25, 50,100, 250, 500	127	y = 0.1655*x+0.0178	0.9993	0.022	0.072
Mn	0, 10, 25, 50,100, 250, 500	104	y = 0.1049*x+0.0073	0.9992	0.012	0.041
Fe	0, 10, 25, 50,100, 250, 500	120	y = 0.1393*x+0.3646	0.9990	0.546	1.820
Co	0, 10, 25, 50,100, 250, 500	111	y = 0.2629*x+0.0080	0.9992	0.002	0.008
Ni	0, 10, 25, 50,100, 250, 500	110	y = 0.0714*x+0.0460	0.9995	0.015	0.049
Cu	0, 10, 25, 50,100, 250, 500	84	y = 0.1901*x+0.0484	0.9988	0.028	0.093
Zn	0, 10, 25, 50,100, 250, 500	131	y = 0.0330*x+0.0414	0.9993	0.467	1.557
As	0, 10, 25, 50,100, 250, 500	100	y = 0.0269*x+2.8807E-004	0.9995	0.003	0.009
Se	0, 10, 25, 50,100, 250, 500	122	y = 0.0023*x+0.0021	0.9999	0.026	0.087
Mo	0, 10, 25, 50,100, 250, 500	101	y = 0.0949*x+0.0023	0.9999	0.003	0.010
Sr	0, 10, 25, 50,100, 250, 500	150	y = 0.1422*x+0.0080	0.9990	0.082	0.273
Zr	0, 10, 25, 50,100, 250, 500	86	y = 0.2679*x+0.0035	0.9995	0.013	0.044
Ag	0, 10, 25, 50,100, 250, 500	88	y = 0.0136*x+5.2351E-004	0.9978	0.003	0.012
Cd	0, 10, 25, 50,100, 250, 500	83	y = 0.0034*x+9.1730E-005	0.9990	0.001	0.002
Sn	0, 10, 25, 50,100, 250, 500	120	y = 0.0083*x+8.6624E-004	0.9996	0.009	0.030
Sb	0, 10, 25, 50,100, 250, 500	87	y = 0.0119*x+3.9589E-004	0.9995	0.002	0.007
Ba	0, 10, 25, 50,100, 250, 500	99	y = 0.0044*x+4.6797E-004	0.9991	0.016	0.053
La	0, 10, 25, 50,100, 250, 500	102	y = 0.6252*x+0.0022	0.9996	0.006	0.020
Hg	0, 2.5, 5, 7.5, 10, 12.5	72	y = 0.0014*x+1.6096E-005	0.9988	0.008	0.027
Pb	0, 10, 25, 50,100, 250, 500	88	y = 0.0169*x+0.0015	0.9991	0.005	0.018

ENFs should adequately fulfil daily nutrient and energy requirements for humans. However, many researchers have reported the deficiency of some metals necessary for humans, in patients fed with ENF for a long time. Gottrand et al. (2013) reported that at least one of the metals Ca, Cu, Fe, Mg, P, Se and Zn were deficient in 94% of children due to long-term ENF use, while Santos et al. (2016) reported that Fe deficiency occurred in approximately 50% of patients who underwent gastrostomy due to long-term ENF use. Iturbide-Casas et al. (2019) reported that the concentration levels detected in ENFs for Fe, Mg, Mn, Zn and Ca were lower than the labelling information. In addition, the presence of some metals with toxic properties, such as Pb, As and Cd in ENFs, has also been reported in different studies (Maziero and Viana, 2022; Menezes et al., 2024).

All these studies indicate that there are some concerns about the nutritional status of patients using ENFs. Therefore, further investigation of metal levels in these artificial formulae is needed to ensure the quality and safety of ENFs (possibility of nutrient deficiency or toxic effects) (Menezes et al., 2024). Although the close association of metals with many diseases has been documented, the number of studies examining metal levels in ENFs and assessing health risks is very limited. In some studies on ENFs, Iturbide-Casas et al. (2019) examined six metals (Ca, Mg, Fe, Zn, Cu and Mn), Anunciação et al. (2021) five metals (K, P, Cu, Fe and Zn), Maziero and Viana (2022) five metals (Al, Cd, Cu, Mo and Pb), Menezes et al. (2024) 13 metals (Ca, Fe, K, Na, P, Zn, As, Al, Cd, Cr, Cu, Mn, and Pb). According to the available literature, to our knowledge, no study has reported Be, Ag, Sn, Sb, Ba, Hg, Li, V, Co, Ni, Se, Sr, Zr and La and making health risk assessments to date. This study aims to (i) determine the levels of 23 metals (Be, Ag, Cd, Sn, Sb, Ba, Hg, Pb, Li, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Sr, Zr, Mo and La) in ENFs developed for adult patients, (ii) identify metal exposure resulting from ENF consumption, and (iii) evaluate the exposure level in terms of non-carcinogenic health.

2. Materials and methods

2.1. Samples

In this study, a total of 28 enteral nutrition formulas with different brands and ingredients were evaluated for heavy metal contamination. All samples have been developed for adult use. Sample 1 − 25 and Sample 26− 28 are in liquid and powder forms, respectively. While the packaging type of Samples 1− 15 and 22− 25 is plastic, the other samples are in tetrapak packaging. Two products from each product with different production and batch numbers were purchased from pharmacies. Samples were analyzed in the laboratory immediately after purchase.

2.2. Analysis of metals

2.2.1. Reagents and standards

All chemicals and reagents used were of analytical reagent grade. 65% HNO_3 (Lot no: Z0804341-222) 30% HCl (Lot no: Z0850018-323) and 35% H_2O_2 (Lot no: K46680900525) were purchased from Supelco (Darmstadt, Germany) and Merck (Darmstadt, Germany), respectively. ICP-CAL2-1 solution (Lot no: 222105034) was purchased from AccuStandard (New Haven, USA), Hg standard solution (Lot no: 0120793620) was purchased AccuStandard (New Haven, USA), Mo standard solution (Lot no: 223025141) was purchased from AccuStandard (New Haven, USA), La standard solution (Lot no: HC16447327) was purchased from Supelco (Darmstadt, Germany), Zr standard solution (Lot no: HC02466670) was purchased from Supelco (Darmstadt, Germany), ICP multi-element standard solution III (Lot no: 51-333CRY2) was purchased from Agilent (Santa Clara, USA), tuning solution (Lot no: 43-90GSX2) and internal standard solution (Lot no: 51-331CRY2) from Agilent (Santa Clara, USA).

2.2.2. Sample preperation and ICP − MS analysis

All ENF samples were prepared by using Microwave digestion system (Milestone Ethos Up, Italy). The “Mixed Samples” method of the Milestone Ethos Up was used for the enteral nutrition formulas. For the digestion process, approximately 1000 mg of the samples were weighed. The 9 ml of HNO_3 and 1 ml of H_2O_2 were added to the weighed samples after that the samples have been sealed with the Ptfe vessels (poly tetra fluoro ethylene high pressure) and incubated in the microwave at 210 °C for 40 min. The samples that removed from the microwave, were cooled for approximately 20 min. Samples were taken into the 15-mL falcon tubes and diluted 15 ml of ultrapure water (Millipore/IQ 7005, Massachusetts, USA). All samples were filtered through a 0.45 μm filter. After that, the elemental analysis was performed in the ICP-MS device. The solution (9 ml of HNO_3 and 1 ml of H_2O_2) was used as the blank solution. Analyses were carried out in three parallel.

7800 Inductively Coupled Plasma Mass Spectrometry (ICP–MS) (Agilent Technologies, Tokyo, JHS, Japan) was used for heavy metal analysis. All glass, quartz and nickel parts (glass micro mist nebulizer (U-series, Australia), quartz spraying chamber (double pass, USA), quartz connector (HMI kit, USA), quartz torch (2.5 mm, Japan), sample cone and skinner cone (for x-lens, USA)) were removed and cleaned according to cleaning procedure before the elemental concentration determination of the enteral nutrition samples.

^{9}Be, ^{107}Ag, ^{114}Cd, ^{118}Sn, ^{121}Sb, ^{137}Ba, ^{201}Hg and ^{208}Pb were quantified in standard mode (no gas), while for ^{7}Li, ^{51} V, ^{52}Cr, ^{55}Mn, ^{56}Fe, ^{59}Co' ^{60}Ni, ^{63}Cu, ^{66}Zn, ^{75}As, ^{78}Se, ^{88}Sr, ^{90}Zr, ^{95}Mo and ^{139}La the He mode which reliably eliminates all common polyatomic interference using kinetic energy discrimination (KED). The system was purged with helium for 45 min before starting the analysis. The system was activated after making the necessary adjustments of the plasma gas: 15 L/min, auxiliary gas: 1 L/min, carrier gas: 1 L/min, makeup/dilution gas: 1 L/min and carrier gas pressure of 1.45 kPa. After the system was activated the torch axis, the resolution axis, the EM, the standard lenses tune, the plasma correction, the full spectrum and the performance report tests were performed respectively. The calibration of the system passing these tests was performed with a tuning solution (1 μg/L Ce, Co, Li, Mg, Tl, Y). The values obtained as a result of the tuning operation were checked and there was not detected any deviation in system. A batch was created for the enteral nutrition samples to be analyzed and the system was commanded. During the analysis, the standard solutions prepared primarily by using the stock solutions were injected and the calibration curves were checked. The analysis was continued after the control of the calibration curves, and the elemental concentrations of the samples have been determined.

Measurements were carried out with power of 1200 W RF, carrier gas flow of 1 L/min and nebulizer pump speed of 0.30 rps. An argon gas was used as carrier gas. 2% HNO_3 and ultra-pure water were used as washing solutions of the system and 1% HCl was used as washing solution of the injector. With the help of "Mass Hunter 4.4 Workstation Software 7800 ICP-MS Top C.01.04", measurements were automatically calculated using the formula [Dilution factor= (Final weight or volume/Sample quantity or volume) × Dilution coefficient] as a ppb.

2.2.3. Quality control

Calibration curves were created different concentrations using stock solutions. The performance of the method was evaluated through recovery experiments by spiking 100 μg/L for Sample 5 and 13. For studied elements, the limit of detection (LOD), limit of quantification (LOQ) and recovery level values were given Table 1. The R^2 prepared with standard solutions of all heavy metals was >0.99. The mean recoveries ranged from 72.2% to 150% for all heavy metals.

2.3. Health risk assessment

2.3.1. Metal exposure

The first stage of health risk assessments is to calculate the exposure of individuals due to ENF consumption. In this study, the deterministic model was preferred to calculate both easy-to-apply and point exposure. ESPEN (The European Society for Clinical Nutrition and Metabolism) recommended starting an enteral nutrition formula in cases where the patient has <60% of the estimated daily energy intake due to insufficient food intake for more than 10 days (Arends et al., 2017). Considering the recommendations of ESPEN, daily heavy metal exposure from consumption of ENFs was calculated for 3 different scenarios, based on the ideal daily energy intake for a healthy adult male and female. As a general approach, the daily energy needs of a healthy adult male and female are approximately 2500 and 2000 kcal/day, respectively. The determined scenarios are; Scenario 1 = 50% oral nutrition +50% ENF, Scenario 2 = 25% oral nutrition +75% ENF and Scenario 3 = 100% ENF. Metal exposure from ENF consumption was calculated using the following formula (Basaran et al., 2024).

Table 2
Levels of metals detected in ENFs (μg/L, mg/L*).

Metals	Fe*	Zn*	Mn	Cu*	Mo	Se
Samples (n = 28)	12 ± 3.3	8.5 ± 2.5	2 ± 0.8	1.3 ± 0.4	75 ± 30	61 ± 21
Metals	**Cr**	**Sr***	**Ba**	**V**	**Ni**	**Co**
Samples (n = 28)	41 ± 19	0.46 ± 0.17	74 ± 103	7.3 ± 2	10 ± 13	1.6 ± 1.6
Metals	**As**	**Li**	**Be**	**Zr**	**Sn**	**Ag**
Samples (n = 28)	1.6 ± 0.6	0.34 ± 0.36	0.05 ± 0.08	<LOD	<LOD	0.02 ± 0.1
Metals	**Cd**	**Sb**	**La**	**Hg**	**Pb**	
Samples (n = 28)	0.14 ± 0.12	0.01 ± 0.1	0.63 ± 0.4	0.05 ± 0.03	0.14 ± 0.7	

$$EDI = \frac{\left(HM_c \times \frac{SCE_x}{ENF_x}\right)}{bw}$$

EDI is the estimated daily metal exposure from ENF (μg/kg bw/day), SCE_x is scenarios based on daily energy intake recommended by ESPEN (kcal/day), ENF_x is energy value of each ENF (kcal/100 mL), HM_c is the concentration of metal in ENF (μg/100 mL), bw is body weight (70 and 80 kg for female and male, respectively).

2.3.2. Target hazard quotient (THQ)

THQ describes the non-carcinogenic health risk posed by exposure to the respective toxic compound. While THQ≥1 indicates a potential health problem that is not carcinogenic, THQ<1 means there is negligible risk about health hazard (Basaran, 2022a). THQ was calculated using the following formula:

$$THQ = \frac{EDI}{RfD}$$

EDI is the estimated daily metal exposure (μg/kg bw/day), RfD is oral reference dose. RfD for Li, Be, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Sr, Zr, Mo, Ag, Cd, Sn, Sb, Ba, La, Hg and Pb is 2×10^{-3}, 2×10^{-3}, 5.04×10^{-3}, 3×10^{-3}, 1.4×10^{-1}, 7×10^{-1}, 3×10^{-4}, 2×10^{-2}, 4×10^{-2}, 3×10^{-1}, 3×10^{-4}, 5×10^{-3}, 6×10^{-1}, 8×10^{-5}, 5×10^{-3}, 5×10^{-3}, 1×10^{-3}, 6×10^{-1}, 4×10^{-4}, 2×10^{-1}, 5×10^{-5}, 1×10^{-4} and 4×10^{-3} mg/kg bw/day, respectively (United States Environmental Protection Agency, 2024; Su et al., 2020).

2.3.3. Hazard index (HI)

The HI assumes that humans are simultaneously exposed to many potentially toxic compounds due to consumption of a particular food. In this case, calculating the cumulative effect of toxic compounds on humans reduces the error in risk assessments (Pekmezci and Basaran, 2024). The HI's evaluation criteria are the same as THQ's criteria. The HI is the sum of the individual THQs of the evaluated items for each ENF and calculated according to the following formula.

$$HI = \sum_{i=1}^{23} THQ_1$$

2.4. Statistical analysis

The analysis were completed by transferring the research data to IBM SPSS Statistics 26 program (*Armonk, New York U.S.A*). While evaluating the data, descriptive statistics (mean ± SD) were given for numerical variables.

3. Results and discusssion

3.1. Levels of metals

The levels of metals identified in the ENFs examined within the scope of the study are shown in Table 2.

3.1.1. Iron (Fe)

The levels of Fe in the samples varied between 1 − 64 mg/L, with an average Fe level of 12 ± 3.3 mg/L across all samples. The highest and lowest average Fe levels were detected in Sample 27 (64 ± 0.7 mg/L) and Sample 26 (1 ± 0.2 mg/L) respectively. The values obtained for Fe in this study were consistent with the declared Fe value on the labels of 11 samples. The average Fe levels in ENFs was reported as 13 mg/L (Iturbide-Casas et al., 2019) and 21.4 mg/L (Menezes et al., 2024) in various studies. However, Anunciação et al. (2021) reported a significantly lower Fe value (2 − 2.9 mg/L) in their study of 3 ENFs compared to this study and other studies in the literature.

3.1.2. Zinc (Zn)

The Zn levels of the samples ranged from 0.6 − 44 mg/L, with an average Zn level of 8.5 ± 2.5 mg/L for all samples. The top three samples with the highest average Zn levels were Sample 27 (41 ± 3.6 mg/L), Sample 12 (15 ± 2.4 mg/L), and Sample 22 (12 ± 2 mg/L), respectively. The values obtained for Zn in this study were in line with the Zn values defined on the labels of 20 samples. The average Zn levels in ENF were reported as 13.2 (11 − 15) mg/L by Iturbide-Casas et al. (2019), 1.7 − 3.1 mg/L by Anunciação et al. (2021), and 10.4 (9.1 − 66) mg/L by Menezes et al. (2024).

3.1.3. Manganese (Mn)

The Mn levels of the samples ranged from 0.11 − 6.7 mg/L, with an average Mn level of 2 ± 0.8 μg/L for all samples. The top three samples with the highest average Mn levels were Sample 12 (6 ± 1 mg/L), Sample 14 (4.6 ± 2 mg/L), and Sample 24 (4 ± 0.4 mg/L), respectively. The values obtained for Mn in this study were lower than the Mn value specified on the labels of 7 samples. Iturbide-Casas et al. (2019) and Menezes et al. (2024) found the average Mn level in ENFs (4.63 and 4.83 mg/L, respectively) to be approximately 2 times higher compared to this study.

3.1.4. Copper (Cu)

The average Cu level of all samples was 1.3 ± 0.4 (0.03 − 4) mg/L. The highest and lowest average Cu levels were found in Sample 27 (3.5 ± 0.7 mg/L) and Sample 28 (0.03 ± 0.01 mg/L) respectively. The Cu levels obtained in this study were lower than the Cu values specified on the labels of 3 samples. The average Cu level in ENFs was reported as 2.53 (2 − 3.3) mg/L (Iturbide-Casas et al., 2019), 0.41 − 0.43 mg/L (Anunciação et al., 2021), and 2.13 mg/L (Maziero and Viana, 2022). The Cu values obtained in this study are consistent with the study by Menezes et al. (2024) (1.39 mg/L).

3.1.5. Molybdenum (Mo)

The average level of Mo in all samples was 75 ± 30 μg/L, with Mo levels in samples ranging from 0.4 − 216 μg/L. The highest and lowest average Mo levels were found in Sample 12 (193 ± 33 μg/L) and Sample 26 (1.3 ± 1.2 μg/L) respectively. In this study, values for Mo were lower than the Mo value defined on the labels of 5 samples. Maziero and Viana (2022) reported Mo levels in ENFs as 140 (70 − 200) μg/L.

3.1.6. Selenium (Se)

The average Se level of all samples was 61 ± 21 μg/L, with Se levels of samples varying between 9 − 199 μg/L. The highest and lowest average Se levels were detected in Sample 27 (165 ± 47 μg/L) and Sample 26 (5 ± 2.5 μg/L) respectively. The values obtained for Se in this study were lower than the labelled Se value in 5 samples. There is no study in the literature reporting the level of Se in ENFs.

3.1.7. Chromium (Cr)

The average Cr level of all samples was 41 ± 19 (LOQ − 122) μg/L. The Cr level of 3 samples was below the LOQ value. The highest average Cr level was found in Sample 25 (121 ± 3 μg/L). In this study, the values obtained for Cr were lower than the Cr value defined on the label of 6 samples. The findings regarding Cr in this study are lower compared to the study by Menezes et al. (2024) (average 87 (21–190) μg/L).

3.1.8. Strontium (Sr)

The Sr levels of the samples varied between 6 − 1329 μg/L, with an average Sr level of 0.46 ± 0.17 mg/L determined for all samples. The average highest and lowest Sr levels were found in Sample 26 (1243 ± 122 μg/L) and Sample 28 (6 ± 0.7 μg/L) respectively. There is no study in the literature reporting the level of Sr in ENFs.

3.1.9. Barium (Ba)

Ba was detected in 86% of the samples examined, and the levels of Ba in Sample 1, 2, 3, and 4 were below the LOQ value. The average Ba level of all samples was 74 ± 103 (<LOQ − 422) μg/L. The highest average Ba level was detected in Sample 7 (374 ± 130 μg/L). There is no study in the literature reporting Ba levels in ENFs.

3.1.10. Vanadium (V)

In 93% of the samples examined, V was detected, with only Sample 1 and 28 having V levels < LOQ. The V levels of the samples ranged from <LOQ − 37 μg/L, with an average V level of 7.3 ± 2 μg/L detected in all samples. There is no study in the literature reporting the level of V in ENFs.

3.1.11. Nickel (Ni)

The Ni levels of the samples ranged from <LOQ − 81 μg/L, and the average Ni level of all samples wasdetermined as 10 ± 13 μg/L. Ni was detected in 75% of the samples. There is no study in the literature reporting Ni levels in ENFs.

3.1.12. Cobalt (Co)

The average Co level of all samples was determined to be 1.6 ± 1.6 (<LOQ − 12) μg/L. In 14% of the samples (Sample 1, 2, 16, and 28), the Co level was found to be lower than the LOQ value. The highest average Co level was detected in Sample 17 (5.9 ± 3.4 μg/L There is no study in the literature reporting the level of Co in ENFs.

3.1.13. Arsenic (As)

The average As level of all samples was 1.6 ± 0.6 (<LOQ − 5.5) μg/L. The first three samples with the highest average As level were Sample 26 (5 ± 0.8 μg/L), Sample 5 (5 ± 1 μg/L) and Sample 22 (5 ± 1 μg/L), respectively. Menezes et al. (2024) found the As level lower than LOQ (0.7 μg/L) in all ENFs examined.

3.1.14. Lithium (Li)

Li was detected only in Sample 28 (Mean = 9.6 ± 2) among the samples examined, and the Li level in all other samples was lower than the LOQ value. The average Li level of all samples was 0.34 ± 0.36 (LOQ − 11) μg/L. There is no study in the literature reporting Li levels in ENFs.

3.1.15. Beryllium (Be)

The average Be level of all samples was 0.05 ± 0.08 μg/L, with Be levels of samples ranged from <LOQ − 0.4 μg/L μg/L. In 57% of the samples examined, Be was detected as < LOQ. The highest average Be level was detected in Sample 6 (0.4 ± 0.03 μg/L). There is no study in the literature reporting the level of Be in ENFs.

Table 3
Levels of metal exposure due to ENF consumption according to daily energy needs (μg/kg bw/day).

Metals	Scenario 1		Scenario 2		Scenario 3	
	Female (1000 kcal)	Male (1200 kcal)	Female (1500 kcal)	Male (1875 kcal)	Female (2000 kcal)	Male (2500 kcal)
Li	0.001	0.001	0.002	0.002	0.002	0.003
Be	0.001	0.001	0.001	0.001	0.001	0.001
V	0.06	0.07	0.10	0.11	0.13	0.14
Cr	0.36	0.38	0.54	0.60	0.73	0.79
Mn	19.5	20.5	29.3	32.0	39.0	42.7
Fe	100	105	150	164	200	219
Co	0.01	0.02	0.02	0.02	0.03	0.03
Ni	0.09	0.09	0.13	0.15	0.18	0.20
Cu	11.7	12.3	17.5	19.2	23.4	25.6
Zn	74.7	78.4	112	123	149	163
As	0.01	0.02	0.02	0.02	0.03	0.03
Se	0.57	0.60	0.85	0.93	1.14	1.24
Sr	4.12	4.33	6.19	6.77	8.25	9.02
Zr	0.00	0.00	0.00	0.00	0.00	0.00
Mo	0.70	0.74	1.05	1.15	1.41	1.54
Ag	0.0001	0.0001	0.0002	0.0002	0.0002	0.0002
Cd	0.001	0.001	0.002	0.002	0.002	0.002
Sn	0.00	0.00	0.00	0.00	0.00	0.00
Sb	0.0002	0.0002	0.0002	0.0003	0.0003	0.0004
Ba	0.82	0.86	1.23	1.34	1.64	1.79
La	0.005	0.006	0.008	0.009	0.011	0.012
Hg	0.0001	0.0002	0.0002	0.0002	0.0003	0.0003
Pb	0.002	0.002	0.002	0.002	0.003	0.003

Scenario 1 = 50% oral nutrition + 50% enteral nutrition formula, Scenario 2 = 25% oral nutrition + 75% enteral nutrition formula and Scenario 3 = 100% enteral nutrition formula.

3.1.16. Zirconium (Zr)

In all samples examined, the Zr level was lower than the LOD value. ENF'lerde There is no study in the literature reporting Zr levels in ENFs.

3.1.17. Tin (Sn)

The Sn level was found to be lower than the LOD value in all samples examined. There is no study in the literature reporting Sn levels in ENFs.

3.1.18. Silver (Ag)

Ag was detected only in Sample 25 (0.2 ± 0.1 μg/L) and Sample 27 (0.2 ± 0.1 μg/L) among the samples examined. The average level of Ag in all samples was 0.02 ± 0.1 (LOQ − 0.5) μg/L. There is no study in the literature reporting the level of Ag in ENFs.

3.1.19. Cadmium (Cd)

Cd was detected in 62% of the samples examined. Cd levels of the samples varied between < LOQ − 1 μg/L, and the average Cd level of all samples was 0.14 ± 0.12 μg/L. The highest average Cd level was determined in Sample 27 (1 ± 0.1 μg/L). It has been reported that the Cd level of ENFs varies between < LOQ (0.01) − 0.6 μg/L (Menezes et al., 2024) and <LOD (0.02) − 8 μg/L (Maziero and Viana, 2022).

3.1.20. Antimony (Sb)

Among the samples examined, Sb (Mean = 0.3 ± 0.5) was detected only in Sample 13. The average level of Sb of all samples was 0.01 ± 0.1 (<LOQ − 0.7) μg/L. There is no study in the literature reporting Sb levels in ENFs.

3.1.21. Lanthanum (La)

La value was not detected in Sample 1 and 20 among the samples examined. The average level of La of all samples was 0.63 ± 0.4 (<LOQ − 3) μg/L. There is no study in the literature reporting La levels in ENFs.

3.1.22. Mercury (Hg)

Among the samples examined, Hg value was detected only in Sample 27 (Mean = 1.5 ± 0.2) The Hg levels of the samples varied between < LOQ − 2 μg/L, and the average Hg level of all samples was 0.05 ± 0.03 μg/L. There is no study in the literature reporting Hg levels in ENFs.

3.1.23. Lead (Pb)

The average Pb levels of all samples was 0.14 ± 0.7 μg/L, and the Cd level of all samples varie between (<LOQ − 4.4) μg/L. Pb was detected in 11% of the samples examined (Samples 7, 9 and 12). Menezes et al. (2024) reported that the mean of Pb level in ENFs ranged from <LOQ (0.13) − 10 μg/L. Maziero and Viana (2022), on the other hand, explained that the mean Pb value 16 (9 − 30) μg/L in ENFs received from commercial pharmacies in Brazil was reported, and that 2 out of 5 samples analyzed exceeded the maximum level (0.01 mg/kg) by Brazilian legislation.

3.2. Risk assessment

3.2.1. Metal exposure

Metal exposure levels resulting from ENF consumption according to body weight of male and female individuals were calculated according to three different scenarios determined according to energy intake and shown in Table 3.

According to the three different scenarios, daily Fe intake resulting from ENF consumption was determined approximately in the range of 7 − 14 and 8.4− 17.5 mg/day for male and female individuals, respectively. Recommended dietary allowance (RDA) values for Fe were reported as 18 and 8 mg/day for adult (19− 50 years old) women and men, respectively (National Institutes Health, 2019). In this case, the contribution rates of Fe intake from ENF consumption to the daily RDA of female and male individuals are 39 − 78 and 105− 220%, respectively. Fe intake from ENF consumption is lower for women and higher for men compared to RDA values. In this study, it can be said that Fe intake from ENF consumption differs considerably between male and female individuals. Fe is an abundant element in the world and is a biologically essential component of all living organisms (Sánchez et al., 2017). The relationship between Fe and human health has been known since ancient times (Briguglio et al., 2020). However, Fe cannot be taken up sufficiently by organisms due to oxides formed by contact with oxygen (Abbaspour et al., 2014). Fe deficiency is a serious public problem causing anaemia (Bathla and Arora, 2022). Today, it is assumed that Fe deficiency causes about half of all anaemia cases (Petry et al., 2016), and it has been reported that excess Fe can cause Parkinson's disease, diabetes and various damages in many organs and systems (Jomova and Valko, 2011; Bjørklund et al., 2020; D'Mello and Kindy, 2020; Gao et al., 2022a).

According to three different scenarios, the daily Zn intake resulting from ENF consumption was approximately in the range of 5.23 − 10.5 and 6.3− 13.1 mg/day for female and male individuals, respectively. RDA values for Zn were reported as 8 and 11 mg/day for adult females and males, respectively (National Institutes Health, 2019). The contribution rates of Zn intakes from ENF consumption to the daily RDA were determined as 65, 98 and 131% for females and 57, 90 and 120% for males for three different scenarios, respectively. Therefore, scenario two is sufficient for daily Zn intake for both male and female individuals. The other scenarios correspond to low or high levels of daily Zn intake. Zn is a very common trace element in nature. It is indispensable for the growth and development of all living organisms (Chasapis et al., 2012). It is the second most abundant transition metal ion in living organisms after Fe (Cuajungco et al., 2021). There is approximately 1.4–2.3 g Zn in an adult human body (Jeng and Chen, 2022). Zn is one of the essential nutrients of considerable importance in terms of public health. It is estimated that Zn deficiency affects approximately 2 billion people worldwide and approximately 0.8 million people die each year worldwide due to health complications related to zinc deficiency (Waqeel and Khan, 2022). Zn, which is a cofactor of more than 300 enzymes, is also a multipurpose trace element involved in the stabilisation of the structure of many proteins (Chasapis et al., 2012). Adequate Zn intake in healthy and sick individuals has many critical roles in human metabolism, such as response to oxidative stress, maintaining the immune system, DNA replication and damage repair, preventing the appearance of skin lesions, and assisting wound healing (Chasapis et al., 2020; Cuajungco et al., 2021; Wu et al., 2022; Costa et al., 2023).

According to three different scenarios, daily Mn intake resulting from ENF consumption was approximately in the range of 1.37 – 2.73 and 1.64– 3.41 mg/day for female and male individuals, respectively. RDA values for Mn were reported as 1.8 and 2.3 mg/day for adult females and males, respectively (National Institutes Health, 2019). The contribution rates of Mn intakes from ENF consumption to the daily RDA were determined as 76, 114 and 152% for women and 71, 111 and 148% for men for three different scenarios, respectively. According to scenario number two, it can be said that daily Mn intake is sufficient for the daily needs of women and men. Scenario number three causes 50% more daily Mn intake. Adequate Mn intake is necessary for defense against oxidative stress, strengthening the immune system and maintaining other physiological processes in human metabolism (Miah et al., 2020). High exposure to Mn leads to manganism disease, which is associated with a syndrome similar to Parkinson's disease (Mattison et al., 2024). Mn deficiency can lead to impairment of the skeletal-bone system, reduced fertility and birth defects, impaired glucose tolerance and various neurodegenerative diseases (Aschner et al., 2005; Soares et al., 2020; Rondanelli et al., 2021; Dai et al., 2021).

According to three different scenarios, the daily Cu intake from ENF consumption was approximately in the range of 0.82 – 1.64 and 0.98– 2.1 mg/day for female and male individuals, respectively. RDA values for Cu were reported as 0.9 mg/day for adult females and males (National Institutes Health, 2019). The contribution rates of Cu intakes from ENF consumption to the daily RDA are 91 – 182 and 108– 227% for men and women, respectively. Therefore, it can be said that scenario 1 is sufficient for men and women in Cu intake from ENF consumption. Scenarios 2 and 3 correspond to a Cu intake much higher than the daily requirement. Cu is an essential microelement for human metabolism (Kamiya, 2022). Since Cu cannot be produced and stored in the human body, it must be regularly taken from water and food (Yang et al., 2022). Cu plays an important role in many physiological and biological processes in human metabolism, including normal growth and development of children, iron metabolism, antioxidant defense and immune function (Bost et al., 2016; Bisaglia and Bubacco, 2020; Grzeszczak et al., 2020; Ruiz et al., 2021; Jomova et al., 2022). Although it is an essential micronutrient for humans, high levels of Cu exposure easily lead to Fenton-type redox reactions, causing oxidative stress, cell death and inflammatory responses (Bost et al., 2016; Kamiya, 2022; Chen et al., 2022).

The daily Mo intake from ENF consumption according to three different scenarios was approximately in the range of 49 – 98 and 60– 120 μg/day for female and male individuals, respectively. The RDA values for Mo are the same for adult men and women and are reported to be 45 μg/day (National Institutes Health, 2019). The contribution rates of Mo intakes from ENF consumption to the daily RDA are 108 – 217 and 131– 267% for men and women, respectively. Therefore, it can be said that Mo intake from ENF consumption is above the daily requirement for men and women in all three different scenarios. Mo is recognised as an important trace element for human health (EFSA Panel on Dietetic Products Nutrition and Allergies, 2013). Evidence of Mo deficiency and toxicity in humans is limited (Novotny, 2011). The tolerable upper intake level for Mo is determined as 2 mg/day (Institute of Medicine Panel on Micronutrients, 2001). Mo has an important role as a cofactor in the functioning of more than 60 enzymes that catalyze chemical reactions involved in the global cycle of N, C and S (Smedley and Kinniburgh, 2017). Four Mo-dependent enzymes are known in humans, each harbouring a pterin-based Mo cofactor (Moco) in the active site (Smedley and Kinniburgh, 2017). In humans, Moco deficiency has been associated with neurological abnormalities and mortality in early childhood (Schwarz, 2016).

The daily Se intake resulting from ENF consumption according to three different scenarios was in the range of approximately in the range of 40 – 80 and 48– 100 μg/day for female and male individuals, respectively. The RDA values for Se are the same for adult women and men, reported as 55 μg/day (National Institutes Health, 2019). The contribution rates of Se intake due to ENF consumption to the daily RDA were determined as 73, 108 and 145% for females and 87, 135 and 182% for males for three different scenarios, respectively. Therefore, considering the daily Se requirement, it can be said that scenario 2 for women and scenario 1 for men are more appropriate. Se has been considered a toxic element for a long time. However, it has been understood that Se is a trace element for living organisms (Schwarz and Foltz, 1957). In recent years, Se has been added to food products to increase the bioavailability of these foods (Basaran, 2022b). It has been reported that Se has a protective effect against diseases, such as cardiovascular diseases and cancer, including COVID-19, (Khatiwada and Subedi, 2021; Kuria et al., 2021; Barchielli et al., 2022), and it has also been explained that selenosis (selenium poisoning) may occur due to high levels of Se intake (Kieliszek and Błażejak, 2016). The NOAEL (No Observed Adverse Effect Level) and LOAEL (Lowest Observed Adverse Effect Level) values for Se were reported to be 0.015 and 0.023 mg/kg/day, respectively (United States Environmental Protection Agency, 1991).

According to three different scenarios, the daily Cr intake resulting from ENF consumption was determined to be approximately in the range of 25 – 51 and 31– 64 μg/day for female and male individuals, respectively. RDA values for Cr were reported as 25 and 35 μg/day for adult females and males, respectively (National Institutes Health, 2019). The contribution rates of Cr intakes from ENF consumption to the daily RDA are 100 – 204 and 90– 182% for men and women, respectively It can be said that the daily Cr intake of scenario 1 is sufficient for the daily needs of male and female individuals. Cr is a component of the glucose tolerance factor and regulates the rate of glucose removal from the blood by increasing insulin activity (Kazi et al., 2008). Cr is also involved in the processing of carbohydrates and fats and pathologies related to weight loss may occur in Cr deficiency (Monga et al., 2022). The International Agency for Research on Cancer has defined Cr (III) in Group 3 (not classifiable as to its carcinogenicity to humans), and Cr (IV) in Group 1 (carcinogenic to humans) (International Agency for Research on Cancer, 2024).

The daily metal exposure levels of women from ENF consumption were determined approximately in the range of 290 – 580, 57– 115, 4.5– 9, 6.3– 13, 1– 2.1, 1– 2.1 μg/day for Sr, Ba, V, Ni, Co and As, respectively, considering three different scenarios. When three different scenarios were considered, the daily metal exposure levels of males from ENF consumption were found approximately in the range of 350 – 720, 70– 140, 5.4– 11, 7.5– 16, 1.3– 2.6, 1.2– 2.6 μg/day for Sr, Ba, V, Ni, Co and As, respectively. The daily exposure levels of Li, Be, Zr, Sn, Ag, Cd, Sb, La, Hg and Pb from ENF consumption of both male and female individuals were less than 1 μg/day for all three scenarios. The tolerable daily intake (TDI) contribution rates of Ni, Ba and Sr intakes from ENF consumption for all individuals (male and female) were $<$19%, $<$9% and $<$7%, respectively. The contribution of V to TDI was $<$0.7%, Cd and Hg $<$0.3%, Li, Be, Ag, Sb and La $<$0.05%. Therefore, the contribution levels of Sr, Ba, V, Ni and Co exposure levels to Provisional tolerable daily intake (PTDI) from ENF consumption are very low, and therefore, the potential health risks are also low. Since TDI values for Pb and As were not determined, the contribution rates of these metals were not calculated.

Sr is mostly deposited in human bones and may promote bone growth and prevent osteoporosis (Marx et al., 2020; Kołodziejska et al., 2021), reduce oxidative stress by exhibiting antioxidant properties (Yalin et al., 2012; Shen et al., 2022), and may also contribute to the treatment of diseases, such as cardiovascular disease, hypertension and diabetes (Ru et al., 2024).

Ba is a non-essential element for terrestrial organisms and is reported to be toxic at high concentrations (Krishna et al., 2020). It has also been reported that high levels of Ba exposure can cause vomiting and diarrhoea, heart and kidney failure, anxiety and nervous system diseases in humans (Kravchenko et al., 2014; Peana et al., 2021).

V has not been shown to be a trace element or to have any nutritional value for humans (Imtiaz et al., 2015). It has been reported that high levels of V exposure may cause irreversible damage to the kidneys (European Food Safety Authority, 2004). It has also been described that V compounds can initiate some gastrointestinal problems, such as diarrhoea, vomiting, general dehydration with weight loss (Wilk et al., 2017).

Ni is safe for most adults in amounts not exceeding 1 mg per day (Goverment of Canada, 2023). However, its relevance to human health is still controversial and high levels of Ni exposure have been reported to have serious adverse effects on human health (Begum et al., 2022). The International Agency for Research on Cancer has identified Ni as possibly carcinogenic to humans in Group 2B (International Agency for Research on Cancer, 2024).

The main role of Co is its integral functionality in the coenzyme vitamin B12 (Jomova et al., 2022). High levels of exposure have been shown in several studies to cause some adverse health effects (Linna et al., 2020; Kovochich et al., 2021).

As exposure is recognised as a global public health concern (Wilson, 2015). The Codex Alimentarius has withdrawn its previous PTWI (Provisional Tolerable Weekly Intake) for As (2.1 μg/kg/day), stating that it is not possible to establish a safe intake limit (The Codex Alimentarius, 2011). As increases the risk of developing various types of cancer, weakens the immune system, leaving individuals vulnerable to diseases, and damages the cardiovascular and nervous systems (Liu et al., 2023; Sen et al., 2023; Rahmani et al., 2023). The International Agency for Research on Cancer has identified arsenic and arsenic compounds as directly carcinogenic to humans in Group 1 (International Agency for Research on Cancer, 2024).

Although Li is not a trace element for humans, low Li intakes have been reported to be associated with suicide, bipolar disorders and aggressive behaviour (Collins et al., 2010; Ishii and Terao, 2018). Li is also an effective psychopharmacological agent widely used in the treatment of neuropsychiatric disorders (Strawbridge et al., 2023). Therefore, dietary intake of Li has been recommended (Naeem et al., 2021).

Be and its compounds have been identified by the International Agency for Research on Cancer as directly carcinogenic to humans in Group 1 (International Agency for Research on Cancer, 2024). It has been described that Be exposure is associated with various types of cancer, especially lung cancer (Wambach and Laul, 2008; Boffetta et al., 2020). In addition, adverse effects of Be on the respiratory system and skin have been shown (Hiller et al., 2023).

The effects of Zr on living organisms are not yet fully known. Zr is neither essential nor toxic in the traditional sense (Ghosh et al., 1992). The daily intake of Zr is estimated to be 4.15 mg (Schroeder and Balassa, 1966). Although the toxicity level has been reported to be low in experimental and clinical studies on Zr (Lee et al., 2010), the relationship between Zr and Alzheimer's disease should be taken into consideration since it can accumulate by crossing the brain barrier (Ghosh et al., 1992; Wang et al., 2021a).

The natural biological role of Sn in living organisms is unknown and it can be poorly absorbed by organisms (Rüdel, 2003). It has also been reported that Sn exposure can cause various health problems in the gastrointestinal tract, such as nausea, vomiting and diarrhoea (Blunden and Wallace, 2003; Granjeiro et al., 2020).

Ag exposure in humans can occur from many sources. Ag is an antibacterial agent used in dermal and mucosal medical applications (Hamad et al., 2020). It has been reported that Ag has a low potential for skin irritation but may cause genotoxicity and further research is needed on its carcinogenic potential (Hadrup et al., 2018). Ag can also accumulate as particles in the human body, causing a blue-grey discolouration known as argyria (Slater et al., 2022).

Cd has long been recognised as an environmental pollutant that poses a risk to human health (Schaefer et al., 2020). It has been described that Cd can accumulate in different organs, especially the liver and kidneys, and can cause cancer (especially lung and prostate cancer) (European Food Safety Authority, 2009), and high levels of Cd exposure have also been associated with impaired cardiovascular and nervous system (Wang et al., 2021b; Zhao et al., 2023). The International Agency for Research on Cancer classified cadmium and cadmium compounds in Group 1 (carcinogenic to humans) (International Agency for Research on Cancer, 2024). The Codex Alimentariusstated that TDI for Cd was 1 μg/kg bw/day (7 μg/kg bw/week) (The Codex Alimentarius, 2011), while European Food Safety Authority (2009) stated as 0.36 μg/kg bw/day (2.5 μg/kg bw/week).

It is controversial whether Sb is a trace element for humans and whether it has harmful effects on human health (Boreiko and Rossman, 2020). Studies have reported that high levels of Sb in the human body may increase the risk of breast and prostate cancer (Kotsopoulos et al., 2012; Shi et al., 2023). It has also been explained that Sb can cause or promote various diseases through cellular or molecular damage (Lai et al., 2022).

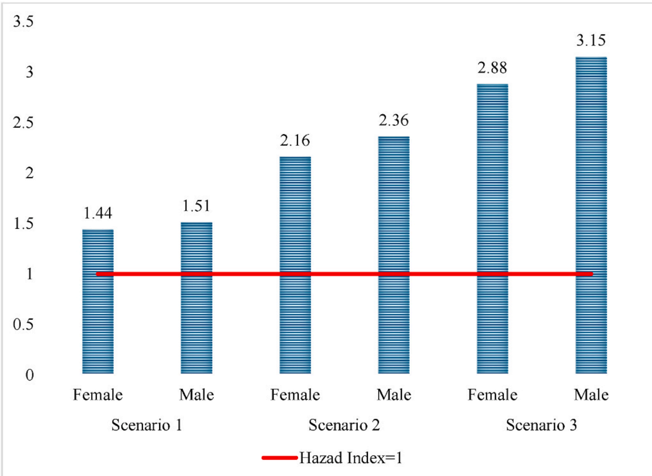
La is administered orally to patients with renal insufficiency as a calcium and aluminum-free phosphate binder (Harrison and Scott, 2004), and it has been reported that long-term exposure to La may have a significant adverse effect on the rate of signal transmission in the human brain, may cause disruption in various tissues, and has been associated with some adverse neurobehaviours (Zhu et al., 1997; Feng et al., 2006; Malvandi et al., 2021).

Hg is a toxic metal not essential in the human body, and its effects on human health are a global concern (Park and Zheng, 2012; Ha et al., 2017). Hg exposure is a serious risk factor for various diseases in many organs and systems (European Food Safety Authority, 2008; Hu et al., 2021; Azar et al., 2021; Gao et al., 2022b). The International Agency for Research on Cancer classified Hg, inorganic mercury in Group 3, whereas it classified methylmercury in Group 2B (International Agency

Table 4
THQ levels of metals.

Metals	Scenario 1		Scenario 2		Scenario 3	
	Female (1000 kcal)	Male (1200 kcal)	Female (1500 kcal)	Male (1875 kcal)	Female (2000 kcal)	Male (2500 kcal)
Li	0.001	0.001	0.001	0.001	0.001	0.001
Be	<0.000	<0.000	<0.000	<0.000	0.001	0.001
V	0.013	0.013	0.019	0.021	0.025	0.028
Cr	0.121	0.127	0.182	0.199	0.242	0.265
Mn	0.139	0.146	0.209	0.229	0.279	0.305
Fe	0.143	0.150	0.214	0.235	0.286	0.313
Co	0.050	0.052	0.074	0.081	0.099	0.108
Ni	0.004	0.005	0.007	0.007	0.009	0.010
Cu	0.292	0.307	0.439	0.480	0.585	0.640
Zn	0.249	0.261	0.373	0.408	0.498	0.545
As	0.049	0.052	0.074	0.081	0.099	0.108
Se	0.114	0.119	0.171	0.187	0.227	0.249
Sr	0.007	0.007	0.010	0.011	0.014	0.015
Zr	<0.000	<0.000	<0.000	<0.000	<0.000	<0.000
Mo	0.141	0.148	0.211	0.231	0.281	0.308
Ag	<0.000	<0.000	<0.000	<0.000	<0.000	<0.000
Cd	0.001	0.001	0.002	0.002	0.002	0.002
Sn	<0.000	<0.000	<0.000	<0.000	<0.000	<0.000
Sb	<0.000	<0.000	0.001	0.001	0.001	0.001
Ba	0.004	0.004	0.006	0.007	0.008	0.009
La	0.108	0.113	0.161	0.177	0.215	0.235
Hg	0.001	0.002	0.002	0.002	0.003	0.003
Pb	<0.000	<0.000	0.001	0.001	0.001	0.001

Scenario 1 = 50% oral nutrition + 50% enteral nutrition formula, Scenario 2 = 25% oral nutrition + 75% enteral nutrition formula and Scenario 3 = 100% enteral nutrition formula.



Scenario 1=50% oral nutrition + 50% enteral nutrition formula, Scenario 2=25% oral nutrition + 75% enteral nutrition formula and Scenario 3=100% enteral nutrition formula.

Fig. 1. HI levels.

for Research on Cancer, 2024). The Codex Alimentarius determined to be PTDI 0.57 μg/kg bw/day for inorganic mercury (The Codex Alimentarius, 2011), and European Food Safety Authority determined to be 0.18 μg/kg bw/day for methylmercury (EFSA Panel on Contaminants in the Food Chain, 2012).

The Codex Alimentarius concluded that it is not possible to establish a safe intake limit for Pb exposure (The Codex Alimentarius, 2011). It has been reported that Pb can cause various diseases in the nervous, cardiovascular, immune, and reproductive systems and organs, such as bone, lungs, kidneys and liver (European Food Safety Authority, 2010; Engwa et al., 2019; Rahman and Singh, 2019). The International Agency for Research on Cancer has classified Pb, inorganic Pb and organic Pb compounds as Group 2B (Possibly carcinogenic to humans), Group 2A (Probably carcinogenic to humans), and Group 3 (Not classifiable as to its carcinogenicity to humans), respectively (International Agency for Research on Cancer, 2024).

The higher the concentration of the metal detected in ENFs, the higher the exposure level of that metal. Since the daily energy requirement of male individuals is higher than female individuals, the metal exposure level resulting from ENF consumption is also higher. Maziero and Viana (2022) reported that ENFs have microelement concentrations exceeding the RDI (Recommended daily intake) and that these elements are of concern in terms of possible toxic effects due to accumulation of these elements in the body.

3.2.2. Non-carcinogenic risk assessment

THQ values of each metal were calculated according to metal exposure levels resulting from ENF consumption (Table 4).

THQ values calculated for each metal in three different scenarios in males and females were lower than the reference value of 1. When the data were analyzed for each metal individually, no alarming findings were found in terms of non-carcinogenic health risks. The ranking of the metals according to THQ values was the same for both male and female individuals and also for three different scenarios. Accordingly, the ranking of metals according to THQ values was Cu > Zn > Fe > Mo > Mn > Cr > Se > La > Co > As > V > Sr > Ni > Ba > Hg > Cd > Li > Pb > Sb > Be > Ag > Zr═Sn. Menezes et al. (2024) explained that the THQ value of three out of nine heavy metals (Pb, Mn and Cr) analyzed in ENFs exceeded 1 in two samples.

Individuals consuming ENFs are exposed not only to one metal but to many metals at the same time. Therefore, HI values were also calculated in the study to evaluate the cumulative effect of all metals (Fig. 1).

The HI levels caused by the total exposure of metals from ENF consumption of both male and female individuals are higher than the reference value of 1 in three different scenarios. Therefore, the cumulative effect of all metals indicates the presence of some potential non-carcinogenic health risks. The top five metals with the highest contribution to HI levels are Cu, Zn, Fe, Mo and Mn, respectively. The total contribution of these five metals to HI levels is approximately 67% and the total contribution of the other 18 metals is approximately 33% (Fig. 2).

Since the daily energy requirement of males is higher than females, they consume higher levels of ENF. This situation causes male individuals to have higher HI levels than females. There is no study analysing the HI level of ENFs in the literature, therefore, the HI values determined in this study were compared with some foods frequently consumed in daily life.

In a study conducted in Türkiye, Basaran et al. (2023) calculated the HI value as 0.81 for the metal (Al, Cr, Mn, Co, Ni, Cu, As, Cd, Hg and Pb) exposure level resulting from the consumption of normally brewed black tea by the general population (>15-year-old). In a recent study conducted in Iraq, the HI value calculated according to metal (As, Cd, Cu, Cr, Pb, Mn, Zn and Fe) exposure levels from tea and coffee consumption was less than 1 and the products were safe in terms of non-carcinogenic health (Ali, 2024). Dippong and Resz (2024) reported that the HI value for the metal (As, Cd, Mn and Pb) exposure level resulting from the consumption of drinking water in Romania was less than 1.

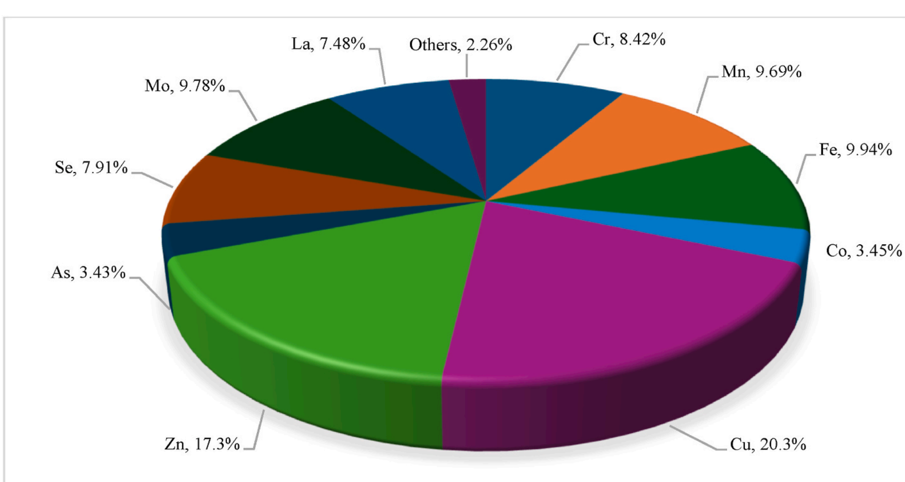


Fig. 2. Contribution rates of metals to HI levels.

4. Conclusion

Considering the potential health risks, metal exposure is recognised as a global public health problem. ENFs are medical foods used for the treatment and prevention of malnutrition, supporting the patient's healing process and many other purposes. In this study, metal levels of some ENFs offered for sale in Türkiye were analyzed and evaluated in terms of health risks. It was determined that ENFs contain some metals known to have toxic effects at different levels. It was found that patients fed with ENFs received insufficient amounts of some microelements necessary for human metabolism and excessive amounts of others. The samples analyzed were evaluated as safe according to THQ values. The average HI level indicates the presence of some health risks in ENFs. All this information raises some health concerns about ENFs. The presence of potential metal contamination from raw materials, water and machinery-equipment used in the production of ENFs suggests that the production processes of ENFs should be reviewed. When this study and other studies in the literature are evaluated together, new and comprehensive studies on metal levels and potential health risks of ENFs should be conducted.

ENFs included in this study may differ from other similar products in terms of formulation and production methods. Therefore, the metal levels detected in ENFs in this study cannot be generalised to all ENFs on the market. In addition, many factors are considered when administering ENFs to patients. It should be noted that this may directly affect metal exposure and associated health risks resulting from ENF consumption.

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CRediT authorship contribution statement

Burhan Basaran: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hulya Turk:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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