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RESEARCH

Health Risk Assessment of Exposure to Heavy Metals in Wheat Flour from Iran Markets: Application of Monte Carlo Simulation Approach

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Abstract

The significance of flour in the Iranian diet underscores the need to ensure its safety from chemical pollutants. This study aimed to evaluate the potential health risks posed by certain heavy metals, such as Fe, Zn, Cu, Al, Co, Hg, Cr, Ni, Pb, and Cd, in wheat flour available in the Iranian market. A total of 248 flour samples were collected from 11 provinces in Iran during the winter of 2021. The health risks associated with heavy metals in children and adults were evaluated using USEPA health risk assessment guidance for superfund part A and Monte Carlo Simulation. The average concentration of Fe, Zn, Cu, Al, Co, Hg, Cr, Ni, Pb, and Cd, was equal to 30.62 ± 59.24, 4.94 ± 13.64, 1.24 ± 3.08, 2.85 ± 4.98, 0.03 ± 0.01, 0.12 ± 0.03, 1.42 ± 1, 0.23 ± 0.05, 1.71 ± 0.65, and 0.02 ± 0.004 mg/kg dry weight, respectively. Analysis of Fe, Cr, Al, Hg and Cr in all flour samples showed that the average concentration of these metals were greater than the standards levels set by the WHO/FAO. The results of the non-carcinogenic risks (HI) showed that the hazard index values (children: 0.969 ± 1.04, adult: 0.837 ± 0.905) of heavy metals through the consumption of flour to both study population were acceptable. The results of the carcinogenic risks (CR) based on Cd, and Pb concentration showed that the CR values from ingestion of flour to the children and adults population were $1.45 \times 10^{-5} \pm 5.08 \times 10^{-5}$ and $1.26 \times 10^{-5} \pm 4.40 \times 10^{-5}$, respectively. The results of Monte Carlo simulation showed that conventional deterministic health risk evaluation could overestimate risk outcomes. Likewise, Cr has 68.8% and 69.1% probability of non-carcinogenic risk to children and adult, respectively, and 80% and 79.8% probability of CR for adults and children respectively for Pb, suggesting that Cr and Pb is a priority control heavy metals. Therefore, it is recommended to continuously monitor the levels of heavy metals in wheat and its derived food products to ensure food safety.

Keywords Heavy metals · Wheat flour · Health risk · Food safety · Environmental pollution

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Introduction

Food safety is a crucial public health concern globally, and foodborne diseases impose a substantial burden on public health, economy, and society each year [1]. According to the report of the World Health Organization (WHO), approximately 10% of the world's population falls ill each year due to unsafe food, leading to 600 million illnesses, 420,000 deaths, and over 33 million healthy life years lost worldwide [1].

Chemical contamination is a worldwide concern for food safety. Many potentially harmful substances present in the environment have the potential to contaminate the food [2, 3]. Heavy metals, which are stable chemical pollutants, are the one of major contaminants found in food globally. Heavy metals are elements with a high specific gravity or atomic number, typically having a specific gravity of > 5–6 g/cm3 or

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an atomic number ranging from 63.5–200 g/mol [4–7]. Some heavy metals, such as Iron (Fe), Copper (Cu), Zinc (Zn), and Manganese (Mn), are essential for human health and play important roles in metabolism and biochemical functions within the human body [8]. However, consuming these elements in concentrations higher than the recommended levels of standards can have adverse effects on human health [5, 9, 10]. On the other hand, non-essential and toxic heavy metals like Lead (Pb), Cadmium (Cd), and Mercury (Hg) can be harmful to human health even in low concentrations [11–15], and the International Agency for Research on Cancer (IARC) has classified these metals as carcinogens in groups 1 and 2, respectively. Heavy metals have garnered attention due to their toxic properties, ability to disperse widely, high resistance to heat, tendency to accumulate in the food chain, and resistance to natural degradation [5, 9, 11, 16]. The consumption of food contaminated with toxic heavy metals is the main way of entering these pollutants into the human body [17, 18].

Wheat is the main food crop in many parts of the world and accounts for 28% of the world's dry matter production and 60% of the daily energy consumption in several developing countries [19]. With an annual per capita consumption of more than 300 kg of wheat flour, Iran has one of the highest rates of wheat flour consumption in the world [20]. Wheat flour is a key ingredient in traditional Iranian breads like Lavash and Taftoon [21]. Consequently, the contamination of wheat flour can have a considerable impact on human health and well-being, particularly in countries undergoing development, such as Iran.

Due to the nutritional significance of flour in the Iranian diet, it is essential to monitor and evaluate the presence of pollutants, such as heavy metals, in this food item. Unfortunately, there is currently no comprehensive study investigating the level of heavy metal contamination in flour in the Iranian market. Previous research has focused on a limited number of metals and examined small samples from one or more provinces of Iran. Therefore, this study aims to comprehensively assess the risk of heavy metal contamination in flour available in the Iranian market through a comprehensive survey of 11 provinces of Iran. Consequently, this study aims to answer the following question: What are the levels of heavy metals in flour available in the Iranian market? Is the concentration of heavy metals in wheat flour higher than the national and international standards? Can the daily consumption of flour in Iran lead to an increase in the risk of cancer and health problems due to the intake of heavy metals in two age groups: children and adults?

Materials and Methods

Sampling, Storage, and Transportation

In this research project, the sample size for analyzing heavy metals was determined using a factorial design. The study focused on 11 provinces (labeled A-K) in Iran that have a significant number of flour factories. A total of 248 flour samples of four type wheat flour (lavash, taftoon,sangak,barbari) were collected from 11 provinces in Iran during the winter of 2021. To ensure accuracy, the analysis was repeated three times, and there was a 13% chance of sample loss; therefore, the final sample size in this study was 248 samples. The collection and assessment of the samples took place during the winter of 2021.

We used pre-washed polyethylene bottles filled with double distilled water to store the samples. All flour samples were carefully transported and stored in dark and cool conditions at 4 °C to prepare for analysis in the laboratory. During this time, we followed official methods of analysis (AOAC, 2012) for sample preparation [22, 23]. Ten grams of flour samples were accurately weighed and dried in an oven at 100 °C to reduce moisture and maintain a constant weight. All dried samples were then homogenized, passed through a 2 mm sieve, and stored in polyethylene bottles at room temperature for further analysis.

Chemical Analysis

For the analysis of heavy metals in flour samples, all acids, reagents, and standard solutions (including stock standard solutions, internal standard solutions, and multi-element solutions) were procured from Merck in Darmstadt, Germany.

The analysis of the flour samples was carried out using inductively coupled plasma-optical emission spectroscopy (ICP-OES). Specifically, the instrument used for this purpose was the Spectro Arcoex model 76,004,555, manufactured in Germany. The analytical procedure followed the EPA 3050B method [23]. To obtain the calibration curve, we utilized blank and standard metal ion solutions. The calibration blank served the purpose of calibrating the ICP-OES with the prepared standards and verifying the absence of interference in the analytical signal. The standard solution was formulated by creating various concentrations of elements, covering a wide range of metal ions. The correlation coefficients of the calibration curves for each metal were greater than 0.99.

Quality Control and Assurance

During the analysis process, glassware and plastic bottles were cleaned by immersing them in diluted nitric acid (HNO_3) for 24 h, followed by rinsing with deionized water. The bottles were then dried at room temperature and stored in tightly sealed containers. The limit of detection (LOD) for wheat flour samples was determined using a standardized method and summerized in Table S1. To evaluate the consistency of the analysis, each sample was measured three times. To ensure the accuracy of the analysis, certified reference materials (CRMs 1567b) and

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standard reference solutions with known element concentrations were employed as control samples. A unit of SRM includs of a single bottle containing approximately 50 g of material sealed inside an aluminized pouch [24]. These CRMs and reference solutions are considered vital tools in guaranteeing the quality and accuracy of heavy metal measurements using ICP-OES [23]. After processing every 10 samples, a control sample was analyzed to validate the accuracy. The recovery rate for each element fell within an acceptable range of 80.46% to 100.55% (Table S1). Recoveries between 80 and 120% were considered satisfactory [25]. The concentrations of all elements were reported as milligrams per kilogram on a fresh weight basis. For further interpretation, the mean concentration of each element was utilized, as repeatability was achieved with a 95% confidence level.

Human Health Risk Assessment

Risk assessment is the process of identifying, analyzing, and evaluating potential risks. This process consists of four stages: hazard identification, dose–response assessment, exposure assessment, and risk characterization [26].

Exposure Assessment

Estimated daily intake (EDI) was applied to assess human exposure dose to heavy metals through direct ingestion wheat flour using Eqs. (1) which were adapted from the US EPA [27]:

$$EDI = \frac{C \times IR \times EF \times ED}{BW \times AT} \quad (1)$$

here EDI is average daily intake dose of heavy metals through ingestion wheat flour (mg kg^{-1} day^{-1}), C is the heavy metals concentration in wheat flour (mg/kg dry weight), an IR is the daily ingestion rate of flour (mg/day), and its average rate for Iranian children and adults is 0.055 and 0.167 mg/day, respectively. Body weight (BW) is the average weight of consumers (child: 16 and Adult: 70 kg), ED shows duration of exposure based years (children: 6 and adults: 30 years), EF is exposure frequency (365 days/year), and AT is averaging time based on days (Table S2).

Non-carcinogenic Risk Assessment

In this study, a non-carcinogenic risk assessment of heavy metals in flour samples was conducted using the Target hazard quotient (THQ) method which is the ratio between EDI and oral reference dose (RfD) of each heavy metal (Table S2). Where RfD indicate "the daily exposure to which the human population could be continually exposed over a lifetime without an appreciable risk of deleterious effects" [28]. RfD (mg/kg.day) for Cd, Ni, Cu, Cr, Fe, Zn, Al, Hg, Co and Pb using 0.001, 0.02, 0.04, 0.003,0.7, 0.3, 0.7, 0.0004, 0.0004 and 0.0035, respectively [29, 30].

$$THQ = \frac{EDI}{RFD} \quad (2)$$

The Hazard Index (HI) was also estimated by summing up the THQ values of each metals to assess the total non-cancer risks based on Eq. 3. When the THQ values are below 1, it indicates a no probability of non-carcinogenic effects for consumers, whereas values above 1 suggest a probability of non-carcinogenic effects [26, 31].

$$HI = \sum \text{THQn} \quad (3)$$

Evaluation of Carcinogenic Risk Exposure

US EPA defined cancer risk (CR) as "the incremental probability of an individual to develop cancer, over a lifetime, as a result of exposure to a potential carcinogen". The assessment of CR was calculated using Eq. 4. Based on USEPA, the values of cancer slope factor (CSF) (mg kg^{-1} day^{-1}) is only assessed for Pb, Cd, and Cr. In this study, CR was estimated based on the Pb and Cd because the others metals were below detection limit.

$$\text{CR} = \text{EDI} \times \text{CFS} \quad (4)$$

where CFS values for Cd and Pb, as provided by the USEPA screening levels, are 0.38, and 0.0085 mg/kg day, respectively [27]. According to the guidelines outlined by USEPA, if the estimated carcinogenic risk values are below 10^{-6}, the risk can be disregarded as negligible. If the values fall within the range of 10^{-4} to 10^{-6}, the risk is considered borderline. However, if the CR value surpasses 10^{-4}, the risk is considered unacceptable, and may poses adverse effects; thus, conducting urgent intervention and remediation is essential [26, 30, 32].

Uncertainty and Sensitivity Analysis

In conventional methods of risk assessment, the risk value is estimated as a single value and reported. This single value cannot provide any information about the uncertainty of the model and its results [33]. To obtain more accurate information about the level of risk or risk ratio, the US EPA has suggested the use of the Monte Carlo simulation method. Monte Carlo simulation utilizes mathematical statistics and probability theory to model uncertainty through random sampling and probability distribution for each input

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variable. Therefore, in this study, Monte Carlo simulation was employed as a probabilistic method to reduce uncertainties. The Crystal Ball software (version 11.1.34190) was used for the Monte Carlo modeling, with 10,000 iterations at a 95% confidence level. The simulated model considered the 95th percentile health risk measure, hazard index, and carcinogenic risk. Another feature of the Crystal Ball software is sensitivity analysis, which was utilized in this study to determine the impact of each change in risk assessment [30, 34].

Statistical Analysis

For statistical analysis, SPSS 19 software was used to process the data in this study. The Kolmogorov–Smirnov test was employed to assess the normality of the data. The one-way ANOVA test was used to compare the concentrations of heavy metals in flour when the data followed a normal distribution, while the Kruskal–Wallis test was used for non-normally distributed data. Descriptive statistics, such as frequency, mean, and standard deviation, were employed to describe the data.

Results and Discussion

Heavy Metals Concentration in Wheat Flour Sample

The results showed that out of the 11 metals studied, iron was detected in 100% of the samples (248 samples), Zn in 98.38% of the samples (244 samples), Al in 91.53% of the samples (227 samples), Cu in 88.70% of the samples (220 samples), Cr in 54.83% of the samples (136 samples), Pb in 23.38% of the samples (58 samples), Co in 13.30% of the samples (33 samples), Ni in 11.83% of the samples (29 samples), Hg in 10.48% of the samples (26 samples), and Cd in 6.85% of the samples (17 samples).

The mean levels of heavy metals in four types of flour (Lavash, Taftoon, Barbari, and Sangak) from 11 provinces of Iran are shown in Fig. 1. The results also showed that the levels of Fe, Cr, Al, Hg, and Pb in all types of flour studied were higher than the standards, and the amount of Zn and Cu in all types of flour were lower than the standards set by the WHO/FAO (Fig. 1).

Lead, a non-essential element for living organisms, possesses toxic properties and can cause serious health consequences when accumulated in humans [35, 36]. Infants and children, due to their higher absorption rate compared to adults, are particularly susceptible to lead poisoning [37, 38]. The contamination of flour with Pb can occur through the equipment used in its production flour [39]. Similar to our results, Olmez et al. showed that the Pb content in flour samples exceeded the standard [40]. However, the results of Noori et al. in 2016 [41] and Pirhadi et al. in 2019 [30] on wheat flour samples in Iran showed that the Pb content was below the recommended limit set by the FAO/WHO. The levels of lead in flour can be influenced by the location where the grains are grown, harvested, and processed. Factors such as proximity to industrial areas, use of contaminated water or soil, and agricultural practices can all impact the levels of lead in the final product [42–44].

Mercury is released to the food chain through mining, and different factories including papermaking plants, using fungicides, waste burning, and industrial/domestic sewage [45]. This toxic element is found in aqueous environments in the forms of metallic Hg, inorganic salt, and organic compounds with different toxicities [46]. Mercury organic compounds are more toxic than its inorganic compounds[35, 47]. This metal enters food through irrigation of agricultural products with water contaminated with various pesticides and industrial effluents [48]. In a study by Basaran et al. in Turkey, the amount of mercury in bread samples was in the range of < LOQ-0.0009 mg/kg [49]. Additionally, the average mercury concentration in all the examined bread samples in Isfahan was estimated to be 0.008 ± 0.01 mg/kg [50].

Chromium (Cr) is found in the environment in two forms: trivalent chromium(III), which is natural and an essential nutrient, and hexavalent chromium (VI), which, is most commonly produced by anthropogenic activities(e.g. industrial sewage discharge, fertilizers, aircraft manufacturing, pesticides, some dyes, and the sewage of plating industries[47, 51]. Wheat has a high capacity for accumulating chromium, making it susceptible to contamination from chromium-contaminated soil and water [52]. Stainless steel equipment used in food processing, such as wheat mills, may also contribute to chromium contamination [53]. The findings of our study align with research conducted in Sulaimani City, where chromium levels of 1.15 mg·kg^{-1} were detected in Turkish white flour samples [54]. However, our results indicate higher chromium concentrations compared to the range of 0.152 to 0.27 mg·kg^{-1} found in wheat flour as reported by Ghanati et al. [55].

Iron is an essential element for the human body and plays a crucial role in various functions including oxygen transfer in erythrocytes, and immunity system enhancement; it also participates in DNA synthesis and electron transfer [56–58]. However, excessive concentrations of iron can lead to tissue damage and an increased risk of cancer development [56–59]. The enrichment of wheat flour with iron is a factor for increased iron levels in bread [23]. Similar to our study, in the study by Khodayi et al. in Isfahan [50] and the study by Ghasemi et al. in Mashhad [23], iron exceeded the limit set by the FAO/WHO.

Aluminum, which is released into the environment through mining and metal industries, may produce side effects [41]. Currently, there is considerable evidence that Al

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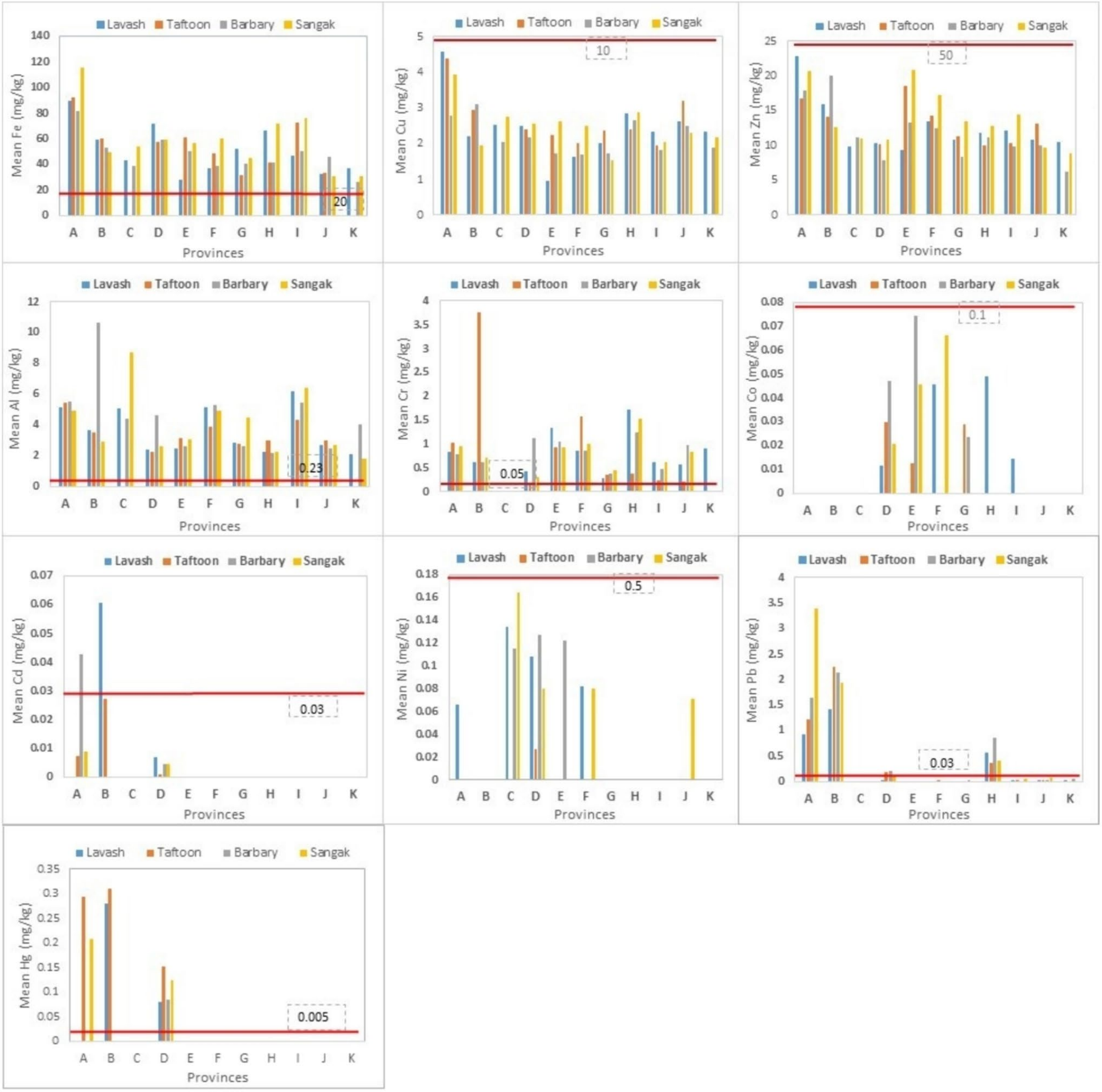

Fig. 1 The concentration of heavy metals (mg/kg) in flour and compared with the standard

may produce side effects[57]. After absorption, aluminum is distributed throughout the body, with higher accumulations in certain tissues such as bones and lungs [41]. Similar to our findings, the aluminum levels in bread samples examined in Isfahan [50] and Mashhad [23] were higher than the standard. Another study reported a high level of aluminum in steam-cooked bread/cake samples in Hong Kong, ranging from 100 to 320 mg/kg [60].

This study assessed 248 flour samples for heavy metal content and found significant variations ($P<0.05$) in Hg, Cu, and Zn concentrations among four types of flour (lavash, taftoon, barbari, sangak)(Table S3). The highest amount of Zn was observed in Sangak flour, while the highest amounts of copper and mercury were found in Taftoon flour.Our finding showed that Sangak flour had the highest amount of Zn, while taftoon flour had the highest amounts of Cu and Hg. Barbari flour had the lowest levels of these metals. This could be due to the outer layer of wheat, which includes the pericarp, bran, and aleurone layer, is richer in minerals and essential elements compared to the inner layer (endosperm). Approximately 61% of total

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minerals are present in the aleurone layer, which tends to be separated during the milling process [30, 61]. Thus, flours with higher extraction percentages, indicating the presence of the aleurone layer, contain more heavy metals [30]. Sangak (93%) and taftoon (87%) flours had the highest extraction percentages, whereas barbari flour had the lowest (82%), resulting in significantly lower amounts of Zn, Cu, and Hg in barbari flour [62, 63]. The varying heavy metal contamination in flours from different provinces of Iran can be attributed to geological, industrial, agricultural, and environmental factors. These factors include differences in soil composition, industrial activities releasing heavy metals into the environment, agricultural practices involving the use of fertilizers and sewage sludge, and environmental conditions such as rainfall and wind patterns [64–67].

Human Health Risk Assessment

According to the results obtained for both study groups (children and adults), the average daily intake rate was Fe > Zn > Al > Cu > Cr > Pb > Ni > Co. The results also showed that the average daily intake of all heavy metals from wheat flour consumption in groups of children and adults was within the permissible daily intake limit.

In this study, since Hg, Cd, Co, Pb, and Ni were only detected in a small percentage of the samples (less than 25%) and the risk assessment results cannot be generalized to our study population, they were not included in the HI. According to our results, the THQ for all heavy metals studied through flour consumption in both children and adults is less than the threshold limit of 1. The results also showed that the HI through flour consumption was in the margin of the permissible value determined by the USEPA (HI < 1) (Table 1).

Table 1 HI and THQ value of heavy metals in children and adults through flour Consumption

Heavy metals	Flour ($n = 248$)	
	Adult	Children
Al	0.012±0.009	0.017±0.013
Pb	0.310±0.922	0.357±1.063
Hg	0.266±1.022	0.306±1.178
Cd	0.008±0.043	0.010±0.050
Co	0.079±0.261	0.090±0.300
Cr	0.387±0.630	0.447±0.726
Cu	0.136±0.083	0.157±0.096
Fe	0.195±0.125	0.225±0.144
Ni	0.003±0.013	0.004±0.015
Zn	0.101±0.044	0.177±0.050
HI*	0.837±0.905	0.969±1.04

N: sample size, ± : standard deviation

*Hg,Pb,Cd,Co and Ni were not included in the HI

The CR of flour samples for children and adults was found to be $1.45 \times 10^{-5} \pm 5.08 \times 10^{-5}$ to $1.26 \times 10^{-5} \pm 4.40 \times 10^{-5}$ (Table 2). Therefore, the carcinogenic risk in all the flour samples studied was at moderate level of risk ($10^{-4} < CR \leq 10^{-6}$).

Wheat flours play a significant role in traditional Iranian breads such as Lavash and Taftoon [68]. Therefore, it is crucial to determine the levels of heavy metals in these flours and assess the associated health risks. The findings of this study revealed that the non-carcinogenic risk of heavy metals from consuming flour did not exceed the acceptable limit of 1 for both children and adults. This indicates that there is no non-carcinogenic risk associated with the consumption of the heavy metals studied in flour. This result is in agreement with the results reported by Noori et al. in Iran, who demonstrated that all estimated values for non-carcinogenic risk of Cd and Pb in wheat flour samples were within the safe range (HI < 1) among all consumers [41]. In the study by Ghanati et al. in Iran, the THQ values of all elements include As, Cd, Co, Cr, Cu, Hg, Ni, Pb, and Zn in various samples such as sweets, wheat flour, wheat, pasta, and bread were found to be less than one, consistent with the findings of the present study [55]. Similar to our study, the results of research by Pirhadi et al. in Iran showed that both adults and children are not at a significant health risk from heavy metals (i.e., Pb, Ni, Cu, As, Zn, Fe, Cr, and Cd) in wheat flour, with a mean THQ and HI < 1 [30].

However, Khodayi et al. in Iran also demonstrated that the HI of heavy metals, including Al, B, Ca, Cr, Cu, Fe, K, Mg, Mn, Na, Se, and Zn, in bread samples was higher than 1. Both children and adults were 5.73 times more at risk of non-cancerous hazards [50].

Similar to our results, Lei et al. [69] conducted a study examining the concentrations of heavy metals (i.e., Hg, As, Cd, Cr, Pb, Cu, Zn, and Ni) in wheat flour samples from the historically irrigated region of Northwest China. Findings indicated that the levels of metallic trace elements did not pose a non-carcinogenic risk in the investigated area, as the HI was below 1, with the exception of children in Jingyang County. In Alemu et al.'s study in 2022 in Ethiopia, both the THQ and HI for the studied metals (Fe, Mn, Cu, Zn, Ni, Cd and Pb) in wheat flour samples were below 1 [70]. The study's findings suggest that the levels of heavy metals detected were

Table 2 Carcinogenic risk of Pb and Cd and total carcinogenic risk (TCR) from flour consumption in the two populations of children and adults ($n = 248$)

Group	Pb	Cd	TCR
Adult	9.23×10^{-6}	3.37×10^{-6}	1.26×10^{-5}
Children	1.06×10^{-5}	3.89×10^{-6}	1.45×10^{-5}

N: sample size, ± : standard deviation

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within safe limits, suggesting no likely health hazards. Wang et al. in China demonstrated that the cumulative health risks associated with heavy metal (Pb, Cd, Cr, As, and Hg) exposure in different grains and grain products were found to be within acceptable levels for both male and female populations, as indicated by HI below 1 for each heavy metal analyzed [71]. Kose et al. in Turkey reported that the HI related to heavy metals induced Mn, Al, Cu, Ni, Pb, As, Cr, Co, Cd, and Hg in bread samples was higher than 1 [72].

However, in a study by Proshad et al. in China, it was revealed that the THQ and HI of Cd, Cr, Cu, Ni, Zn, Fe, Pb, Co, As, Mn, and Ba in analyzed foodstuffs exceeded the standard limits for both adults and children, indicating significant non-carcinogenic health risks [73]. Research conducted by Bassaran in Turkey showed that the THQ for heavy metals including Al, Cr, Mn, Cu, Ni, Co, Pb, As, Cd, and Hg was below 1. However, the hazard index value exceeded 1 for all types of bread [49]. The variation in the results could be influenced by factors such as the types of heavy metals present, the physicochemical characteristics of the soil under study, the geographical location, and the types of products analyzed [30, 50].

The EPA defines cancer risks (CR) as the incremental likelihood of an individual developing cancer over their lifetime due to exposure to a potential carcinogen [28]. A risk level of 1×10^{-6} is typically regarded as the threshold for excess cancer risk, representing a 1 in 1,000,000 chance of developing cancer from consuming wheat flour contaminated with toxic metals at specified levels over a 70-year period [74]. Carcinogenic risks should ideally be maintained below this threshold. EPA guidelines indicate that risks falling within the range of 1×10^{-4} to 1×10^{-6} are considered borderline, with risks exceeding 1×10^{-4} deemed unacceptable. A carcinogenic risk level of 1×10^{-4} is considered significant in terms of health hazards, necessitating intervention and remediation measures [28].

Based on the results presented in this study and comparing the values of CR with the maximum acceptable risk proposed by the EPA, the carcinogenic risk of Pb and Cd in all the flour samples studied was at moderate level of risk ($10^{-4}<CR\leq10^{-6}$). In agreement with our results, Lei et al. [69] studied the carcinogenic risk associated with Cd concentration in wheat flour consumption, revealing a potential adverse health risk for consumers. In a study by Noori et al., cancer risk values determined for Cd were generally in the unsafe range, indicating that there was CR for all consumers due to the ingestion of Cd contained in wheat flour in this study area.

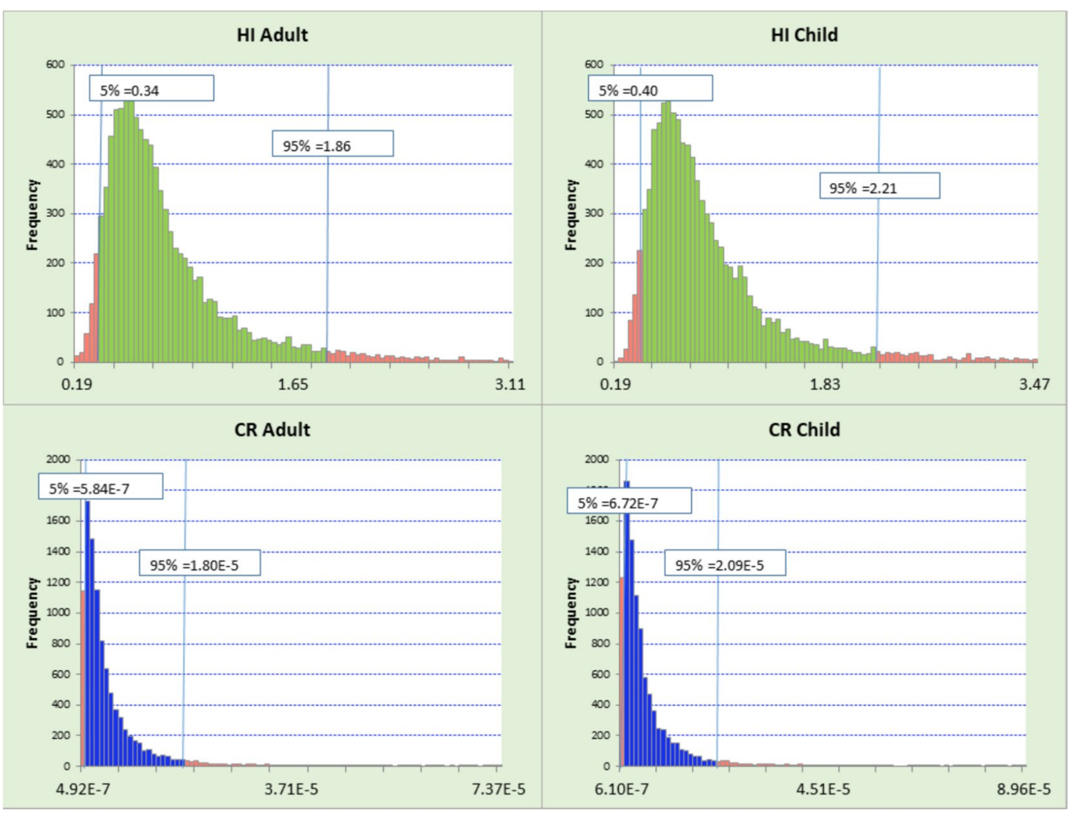

Fig. 2 The cumulative distribution of non-carcinogenic and carcinogenic risk index of heavy metals in children and adults through flour consumption

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Uncertainty and Sensitivity Analysis

The HI of flour consumption was evaluated by Crystal Ball software with 10,000 iterations, considering appropriate confidence intervals (95%). In health risk assessment, all actions should be considered conservatively, therefore in the present study, the 95th percentile was considered as the action level. As shown in Fig. 2, with 95% confidence, the HI for children and adults through flour consumption are 0.40 to 2.21 and 0.34 to 1.86, respectively, which are in the margin of the permissible value determined by the USEPA (HI < 1). The CR for children and adults through flour consumption are 6.72×10^{-7} to 2.09×10^{-5} and 5.84×10^{-7} to 1.80×10^{-5}, respectively.

Sensitivity analysis was conducted to assess the impact of variables such as metal concentration, flour consumption rate, exposure duration, and body weight on the health risk index and carcinogenicity. By utilizing sensitivity analysis, we can determine the extent to which a variable influences the outcome. As shown in Fig. 3, the results of sensitivity analysis indicate that the HI of flour consumption in children and adult populations 68.8–69.1% was influenced by Cr concentration, while other parameters had less than a 15% impact. Also, the results of sensitivity analysis showed that the CR of flour consumption in children and adult populations is 79.8–80% influenced by Pb concentration by 79.8–80%.

According to our results, the greatest effect on the risk of carcinogenic and non-carcinogenic effects was related to the amount of heavy metals such as Pb and Cr in wheat flour, while other variables such as body weight and per capita consumption of wheat flour had less effect. Similar findings were reported by Sharafi et al. (2019) [75], Wang et al. (2020 and 2022) [76, 77], and Liu et al. (2020) [78] which showed that the most influential variable on the HI was heavy metals concentration in cereal. Therefore, even considering various variables such as the per capita consumption of cereals and the body weight of consumers, reducing the contamination of cereals with heavy metals, especially Pb and Cr, can have the greatest effect in reducing the health risks associated with consumption of cereals.

Limitation

Risk assessment has certain limitations. For instance, the estimation of wheat flour consumption and body weight was conducted in accordance with EPA standards. Furthermore, assuming that CSF remains constant for all individuals may not accurately represent the variability among people.

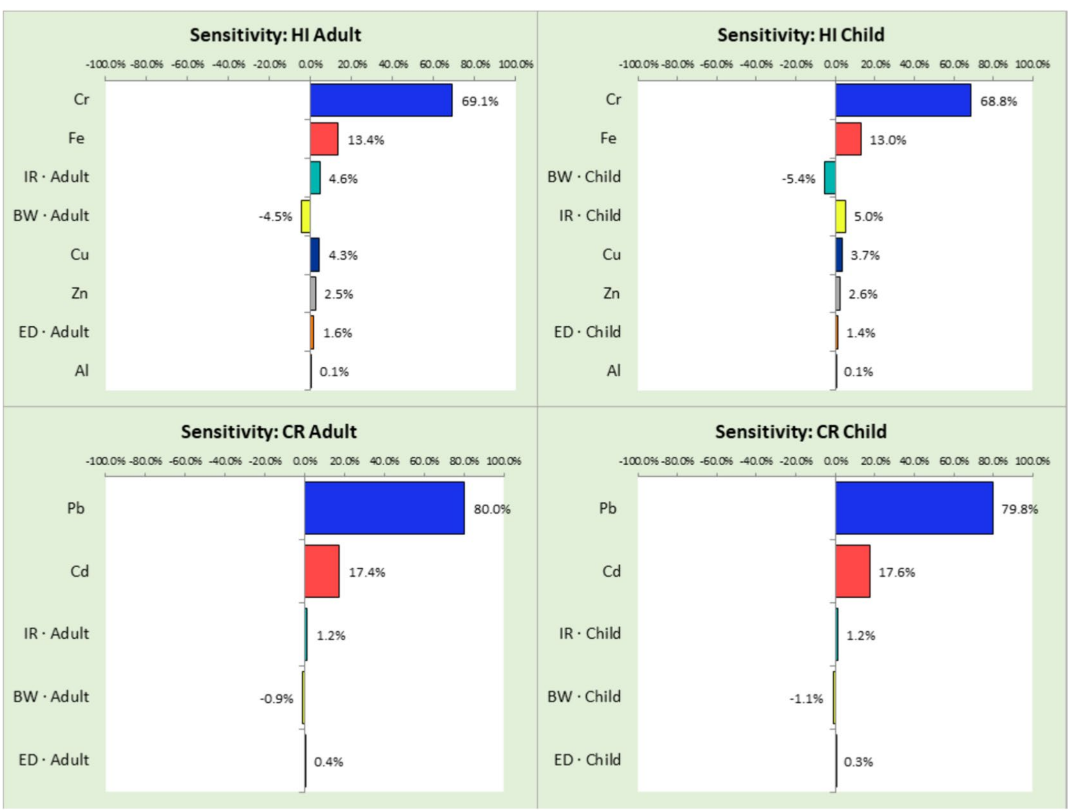

Fig. 3 The effect of different variables on non-carcinogenic and carcinogenic risk index caused by flour consumption in children and adults

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Additionally, the risk assessment model concentrated only on heavy metal concentrations in wheat flour, neglecting the possible existence of other chemical contaminants. As a result, the hazard level of wheat flour in the Iranian market could be higher than what was identified in the present study.

Conclusion

The findings indicated that the levels of Pb, Fe, Cr, Al, Hg, and Hg in flour exceeded both national and international standards. This suggests that the presence of heavy metals in the flour consumed in Iran may have negative effects on consumer health. The risk assessment revealed no non-carcinogenic risk associated with heavy metals through flour consumption in both children and adults. Furthermore, the HI through flour consumption was within the threshold limit of 1. The CR of flour samples for children and adults was found to be $1.45 \times 10^{-5} \pm 5.08 \times 10^{-5}$ to $1.26 \times 10^{-5} \pm 4.40 \times 10^{-5}$. Therefore, the carcinogenic risk in all the flour samples studied was at moderate level of risk ($10^{-4} < CR \le 10^{-6}$). In terms of sensitivity analysis results, taking into account various variables like per capita wheat flour consumption and consumer body weight, decreasing the contamination of wheat flour with heavy metals, particularly Pb and Cr, can have the most significant impact on reducing health risks linked to wheat flour consumption. However, as pollution continues to increase, there is a possibility of further risk escalation over time. Therefore, it is recommended to regularly monitor the heavy metal content and chemical residues in wheat and its food products to ensure food safety.

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Author Contributions F.A. and B.T. wrote manuscript and analyze data. M.GH. contributed to the study design, su-pervised the study. S.KH. and A.A. revised manuscript. M.H. designed the study, supervised the study, and revise to manuscript writing. All authors reviewed the manuscript.

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Data Availability No datasets were generated or analyzed during the current study.

Declarations

Ethics Approval and Consent to Participate The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (#IR.MUMS.REC.1400.351) after obtaining the required permit for the research.

Competing Interests The authors declare no competing interests.

References

1. Tong W, Tao G, Wu Y, Chen X, Leng Y, Huang X, Xiong Y (2023) Aggregation of noble metal nanoparticles: A versatile sensing strategy for food safety monitoring. Trends Food Sci Technol 142:104243
2. Thompson LA, Darwish WS (2019) Environmental chemical contaminants in food: review of a global problem. J Toxicol 2019:1–14
3. Tehrani GM, Tavakoly Sany SB, Hashim R, Salleh A (2016) Predictive environmental impact assessment of total petroleum hydrocarbons in petrochemical wastewater effluent and surface sediment. Environ Earth Sci 75:1–13
4. AbdElgawad MM (2020) Contamination and health risks of certain heavy metals and trace elements in milk and milk products consumed in province of monufia, Egypt. Ann Agric Sci Moshtohor 58(3):673–682
5. Eftekhari M, Shahrami E, Hadi Tavatori M, Atlasbaf M (2022) Assessment of milk contamination by some heavy metals (lead, cadmium, chromium, nickel and mercury) of dairy cattle herd in Qazvin province and its effects on human health. Vet Res Biol Products 35(1):131–137
6. Shar Z, Pirhot O, Shar H, Channa M (2021) Assessing the risk of heavy metals contamination in milk from Pakistan. Int J Sci Res Arch 3(01):107–113
7. Hashemi M, Sadeghi A, Saghi M, Aminzare M, Raeisi M, Rezayi M, Sany SBT (2019) Health risk assessment for human exposure to trace metals and arsenic via consumption of hen egg collected from largest poultry industry in Iran. Biol Trace Elem Res 188:485–493
8. Oftadeh BZ, Sany SB, Alidadi H, Zangouie M, Barati R, Naseri A, Tafaghodi M (2021) Heavy Metals Contamination and Distribution in Drinking Water from Urban Area of Mashhad City in Northeast Iran: Implications for Water Quality Assessment. J Chem Health Risks 11(4):403–418
9. Shahbazi Y, Ahmadi F, Fakhari F (2016) Validation of sequential cathodic-anodic stripping voltammetric determination of ultratrace level of copper, lead, cadmium, zinc, and selenium in milk and dairy products of Iran. Anal Bioanal Electrochem 8(8):948–961
10. Elbagermi MA, Haleem AB, Elsherif KM (2020) Evaluation of essential and heavy metal levels in pasteurized and long-life cow milk. Int J Adv Chem 8(1):6–14
11. Sant'Ana MAR, 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 Chem 346:128961
12. Feizi R, Hamidi F, Jaafarzadeh N, Ghahrchi M, Zafarzadeh A (2022) Determination and health risk assessment of heavy metals (Pb, Cd, Cu and Zn) in different brands of pasteurized milk. Int J Environ Anal Chem 102(18):6892–6903
13. Shahbazi Y, Ahmadi F, Fakhari F (2016) Voltammetric determination of Pb, Cd, Zn, Cu and Se in milk and dairy products collected from Iran: An emphasis on permissible limits and risk assessment of exposure to heavy metals. Food Chem 192:1060–1067
14. Sadeghi N, Behzad M, Homay Razavi S, Jannat B, Oveisi MR, Hajimahmoodi M (2020) Measurement of zinc, copper, lead, and

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cadmium in the variety of packaging milk and raw milk in Tehran markets by anodic striping voltammetry. J Chem Health Risks 10(3):175–183
15 AsadiTouranlou F, Raeesi A, Rezaei M (2024) Health risk assessment of the concentration of heavy metals in Pistacia species: a global systematic review. Nutr Food Sci 54:468–482
16 Birghila S, Dobrinas S, Stanciu G, Soceanu A (2008) Determination of major and minor elements in milk through ICP-AES. Environl Eng Manag J (EEMJ) 7(6):805–808
17. Fakhreddini M, Tabib K, Amidi S, Kobarfard F, Tabatabai SA (2019) Simultaneous measurement of lead and cadmium in the milk distributed in Tehran's schools by differentialpulse anodic stripping voltammetry. Int Pharm Acta 2:e3
18. Rahati S, Hashemi M, Orooji A, Afshari A, Sany SBT (2024) Health risk assessments of heavy metals and trace elements exposure in the breast milk of lactating mothers in the Northeastern Iran. Environ Sci Pollut Res 31(17):25892–25906
19. Wang S, Yin L, Tanaka H, Tanaka K, Tsujimoto H (2011) Wheat-Aegilops chromosome addition lines showing high iron and zinc contents in grains. Breed Sci 61(2):189–195
20. Badakhshan H, Moradi N, Mohammadzadeh H, Zakeri MR (2013) Genetic variability analysis of grains Fe, Zn and beta-carotene concentration of prevalent wheat varieties in Iran. Int J Agric Crop Sci 6(2):57
21. Kamalabadi M, Kamankesh M, Mohammadi A, Hadian Z, Ferdowsi R (2019) Contamination and daily intake of polycyclic aromatic hydrocarbons in Iranian bread samples. Polycycl Aromat Comp 40(4):1187–1195
22. Moyo NA, Rapatsa MM (2019) Trace metal contamination and risk assessment of an Urban River in Limpopo Province, South Africa. Bull Environ Contam Toxicol 102:492–497
23. Ghasemi S, Hashemi M, Gholian Aval M, Khanzadi S, Safarian M, Orooji A, Tavakoly Sany SB (2022) Effect of baking methods types on residues of heavy metals in the different breads produced with wheat flour in Iran: A case study of Mashhad. J Chem Health Risks 12(1):105–113
24. May W, Parris R, Beck C, Fassett J, Greenberg R, Guenther F, Kramer G, Wise S, Gills T, Colbert J (2000) Definitions of terms and modes used at NIST for value-assignment of reference materials for chemical measurements. NIST Spec Publ 260:136
25. Zhou M-H, Tian W, Zhang J-Q, Chen X, Wu Y-X, Wang S-X (2019) A rapid on-site analysis method for the simultaneous extraction and determination of Pb 2+ and Cd 2+ in cereals. RSC Adv 9(56):32839–32847
26. Javedan G, Ghaffari HR, Heidarinejad Z, Zeraei N, Hoseinvandtabar S, Pourramezani F, Ahmadi M (2022) Concentration of potentially toxic elements in black tea imported to Iran: a potential risk assessment study. Iran J Health Saf Environ 15(1):fa153–fa168
27. Epa US (2011) Exposure factors handbook. Office Res Dev Washington, DC 20460:2–6
28. Alidadi H, TavakolySany SB, ZarifGaraatiOftadeh B, Mohamad T, Shamszade H, Fakhari M (2019) Health risk assessments of arsenic and toxic heavy metal exposure in drinking water in northeast Iran. Environ Health Prev Med 24:1–17
29. Ghaffari HR, Kamari Z, Ranaei V, Pilevar Z, Akbari M, Moridi M, Khedher KM, Fakhri Y, Khaneghah AM (2021) The concentration of potentially hazardous elements (PHEs) in drinking water and non-carcinogenic risk assessment: A case study in Bandar Abbas, Iran. Environ Res 201:111567
30 Pirhadi M, Alikord M, Tajdar-Oranj B, Khaniki GJ, Nazmara S, Fathabad AE, Ghalhari MR, Sadighara P (2022) Potential toxic elements (PTEs) concentration in wheat and flour products in Iran: A probabilistic risk assessment. Heliyon 8(11):e11803
31. Kamari Z, Alipour V, Dindarloo K, Fazlzadeh M, Ghanbarnejad A, Ghaffari HR (2022) Assessing the Risk of Carcinogenesis Caused by Exposure to Heavy Metals Through the Consumption of Drinking Water (A Case Study of Bandar Abbas Drinking Water). J Prev Med 9(1):90–101
32. Pirsaheb M, Hadei M, Sharafi K (2021) Human health risk assessment by Monte Carlo simulation method for heavy metals of commonly consumed cereals in Iran-Uncertainty and sensitivity analysis. J Food Compos Anal 96:103697
33. Tajdar-Oranj B, Shariatifar N, Alimohammadi M, Peivasteh-Roudsari L, Khaniki GJ, Fakhri Y, Mousavi Khaneghah A (2018) The concentration of heavy metals in noodle samples from Iran's market: probabilistic health risk assessment. Environ Sci Pollut Res 25:30928–30937
34. Khazaei S, Talebi Ghane E, Bashirian S, Mehri F (2023) The concentration of potentially toxic elements (PTEs) in fruit juices: a global systematic review, meta-analysis and probabilistic health risk assessment. Int J Environ Anal Chem 103(6):1259–1271
35. Fu Z, Xi S (2020) The effects of heavy metals on human metabolism. Toxicol Mech Methods 30(3):167–176
36. Chenouf A, Chenouf N, Bouzidi A, Gaucheron F, Mati A (2016) Heavy metals in small ruminant's milk from Algerian area steppe. Int Food Res J 23(3):1012–1016
37. Tunegová M, Toman R, Tančin V (2016) Heavy metals-environmental contaminants and their occurrence in different types of milk. Slovak J Animal Sci 49(3):122–131
38. Mihretu T (2018) Determination of the levels of selected trace heavy metals and fat content in commercially available milk brands in Addis Ababa city, 7(2):112–120
39. Ghoreishy F, Salehi M, Fallahzade J (2019) Cadmium and lead in rice grains and wheat breads in Isfahan (Iran) and human health risk assessment. Hum Ecol Risk Assess Int J 25(4):924–934
40. Ölmez E, Gökmeşe E, Ergun Ü, Gokmeşe F (2023) Monitoring of lead and some heavy metals in wheat flour of Corum province, Turkey: An air quality comparison. Hittite J Sci Eng 10(1):49–56
41. Aguilar F, Autrup H, Barlow S, Castle L, Crebelli R, Dekant W, Engel K, Gontard N, Gott D, Grilli S (2008) Safety of aluminium from dietary intake scientific opinion of the panel on food additives, flavourings, processing aids and food contact materials (AFC). EFSA J 754:1–34
42. Doddabematti Prakash S, Rivera J, Sabillón L, Siliveru K (2024) From wheat grain to flour: a review of potential sources of enteric pathogen contamination in wheat milled products. Crit Rev Food Sci Nutr 6(2):1–11
43. Bouida L, Rafatullah M, Kerrouche A, Qutob M, Alosaimi AM, Alorfi HS, Hussein MA (2022) A review on cadmium and lead contamination: Sources, fate, mechanism, health effects and remediation methods. Water 14(21):3432
44. Wei J, Cen K (2020) Contamination and health risk assessment of heavy metals in cereals, legumes, and their products: A case study based on the dietary structure of the residents of Beijing, China. J Clean Prod 260:121001
45. Rose M, Baxter M, Brereton N, Baskaran C (2010) Dietary exposure to metals and other elements in the 2006 UK Total Diet Study and some trends over the last 30 years. Food Addit Contam 27(10):1380–1404
46. Aliasgharpour M, Rahnamaye Farzami M (2013) Trace elements in human nutrition: a review. Int J Med Investig 2(3):0
47. COT (2008) COT Statement on the 2006 UK Total Diet Study of Metals and Other Elements. In: HMSO London (UK)
48. Albaji A, Ziarati P, Shiralipour R (2013) Mercury and Lead contamination study of drinking water in Ahvaz, Iran. Intl J Farm and Alli Sci 2:751–755
49. Basaran B (2022) Comparison of heavy metal levels and health risk assessment of different bread types marketed in Turkey. J Food Compos Anal 108:104443
50. Khodaei SM, Esfandiari Z, Sami M, Ahmadi A (2023) Determination of metal (oids) in different traditional flat breads distributed in

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Isfahan city, Iran: health risk assessment study by Latin hypercube sampling. Toxicol Rep 10:382–388
51. Ukhurebor KE, Aigbe UO, Onyancha RB, Nwankwo W, Osibote OA, Paumo HK, Ama OM, Adetunji CO, Siloko IU (2021) Effect of hexavalent chromium on the environment and removal techniques: a review. J Environ Manage 280:111809
52. Gupta N, Yadav KK, Kumar V, Kumar S, Chadd RP, Kumar A (2019) Trace elements in soil-vegetables interface: translocation, bioaccumulation, toxicity and amelioration-a review. Sci Total Environ 651:2927–2942
53. Mathebula MW, Mandiwana K, Panichev N (2017) Speciation of chromium in bread and breakfast cereals. Food Chem 217:655–659
54. Ali Abdul N, Mahmood Abdulrahman A, Talb SS, Mhamad HJ (2023) Mineral processing impact on wheat and barley (Tiry bread and samoon as an example). Mesop J Agric 51(2):36–50
55. Ghanati K, Zayeri F, Hosseini H (2019) Potential health risk assessment of different heavy metals in wheat products. Iran J Pharm Res: IJPR 18(4):2093
56. Aras NK, Ataman OY (2007) Trace element analysis of food and diet. Royal Society of Chemistry
57. Boudebbouz A, Boudalia S, Bousbia A, Habila S, Boussadia MI, Gueroui Y (2021) Heavy metals levels in raw cow milk and health risk assessment across the globe: A systematic review. Sci Total Environ 751:141830
58. Meshref AM, Moselhy WA, Hassan NE-HY (2014) Heavy metals and trace elements levels in milk and milk products. J Food Meas Charact 8:381–388
59. Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowda KN (2014) Toxicity, mechanism and health effects of some heavy metals. Interdiscip Toxicol 7(2):60
60. Wong WW, Chung SW, Kwong K, Yin Ho Y, Xiao Y (2010) Dietary exposure to aluminium of the Hong Kong population. Food Addit Contam 27(4):457–463
61. Khaniki GRJ (2005) Determination of zinc contents in Iranian flat breads. Pak J Nutr 4(5):294–297
62. Shockravi S, Almgren A, Carlsson NG, Sandberg AS (2012) Dephytinisation of Sangak and Barbari bread made from different extraction rate flours increases iron and zinc bioaccessibility in Caco-2 cells. Int J Food Sci Technol 47(11):2252–2258
63. Mohammadbeigi A, Salehi A, Izanloo H, Ghorbani Z, Vanaki V, Ramazani R, Asadi-Ghalhari M (2018) Prevalence of using baking soda in different types of most commonly consumed breads by Iranian people. Adv Hum Biol 8(1):24–27
64 Galavi M, Jalali A, Ramroodi M, Mousavi SR, Galavi H (2010) Effects of treated municipal wastewater on soil chemical properties and heavy metal uptake by sorghum (Sorghum bicolor L.). J Agric Sci 2(3):235
65. Visser A, Kroes J, van Vliet MT, Blenkinsop S, Fowler HJ, Broers HP (2012) Climate change impacts on the leaching of a heavy metal contamination in a small lowland catchment. J Contam Hydrol 127(1–4):47–64
66. Mousavi M, Purnia M, Amiri F (2013) Distribution of heavy metals in agricultural soils around factory of Karoon Cement, South-East Masjed Soleiman. J Geochem 3:215–226
67. Khan S, Cao Q, Zheng Y, Huang Y, Zhu Y (2008) Health risks of heavy metals in contaminated soils and food crops irrigated with wastewater in Beijing, China. Environ Pollut 152(3):686–692
68. Anvari Z (2020) Cultural obstacles to changing social food taste of iranians; case study: to change the taste from traditional to bulky bread. Pertanika J Soc Sci Hum 28(1):78–83
69. Lei L, Liang D, Yu D, Chen Y, Song W, Li J (2015) Human health risk assessment of heavy metals in the irrigated area of Jinghui, Shaanxi, China, in terms of wheat flour consumption. Environ Monit Assess 187:1–13
70. Alemu WD, Bulta AL, Doda MB, Kanido CK (2022) Levels of selected essential and non-essential metals in wheat (Triticum aestivum) flour in Ethiopia. J Nutr Sci 11:e72
71. Wang P, Wang X, Wang H, Zhang G (2024) Health risk assessment of heavy metals from grains and grain products in Gansu Province, China, 2012–2020. J Food Compos Anal 125:105851
72. Köse BG, Pekmezci H, Basaran B (2024) Bread Consumption-Induced Heavy Metal Exposures and Health Risk Assessment of Pregnant Women: Turkey. Biol Trace Elem Res 202(2):473–480
73. Proshad R, Idris AM (2023) Evaluation of heavy metals contamination in cereals, vegetables and fruits with probabilistic health hazard in a highly polluted megacity. Environ Sci Pollut Res 30(32):79525–79550
74. Saha N, Rahman MS, Ahmed MB, Zhou JL, Ngo HH, Guo W (2017) Industrial metal pollution in water and probabilistic assessment of human health risk. J Environ Manage 185:70–78
75. Sharafi K, Nodehi RN, Yunesian M, Mahvi AH, Pirsaheb M, Nazmara S (2019) Human health risk assessment for some toxic metals in widely consumed rice brands (domestic and imported) in Tehran, Iran: uncertainty and sensitivity analysis. Food Chem 277:145–155
76. Wang Y, Tian C, Wang Z, He D, Wu N, Zhang H, He S, Pan L, Ying C (2021) Health risk and temporal trend of dietary potentially toxic elements exposure in the residents of the Shenzhen metropolis, China, between 2005 and 2017: a risk assessment based on probabilistic estimation. Environ Geochem Health 43:113–126
77. Wang Y, Cao D, Qin J, Zhao S, Lin J, Zhang X, Wang J, Zhu M (2023) Deterministic and Probabilistic Health Risk Assessment of Toxic Metals in the Daily Diets of Residents in Industrial Regions of Northern Ningxia, China. Biol Trace Element Res 201(9):1–15
78. Liu P, Zhang Y, Feng N, Zhu M, Tian J (2020) Potentially toxic element (PTE) levels in maize, soil, and irrigation water and health risks through maize consumption in northern Ningxia, China. BMC Public Health 20(1):1–13

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