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ORIGINAL ARTICLE

Measurement of the Toxic Trace Elements in Commercial Wheat Flours: Potential Health Risk via Dietary Intake

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KEYWORDS

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ABSTRACT: Heavy metals contamination is a major concern because of its serious threat to human health. The primary aim of this study was to examine potential health risks for national (adults and children) and international (Arab population) inhabitants that were exposed to heavy metals (Cd and Pb) through ingestion of wheat flour. A total of 300 wheat flours samples (<0.25 mm) of five commercial brands have been collected from 2016 to 2018 from Khuzestan province, Iran. The possible health risk was estimated based on the Hazard Quotient (HQ), hazard index (HI or non-carcinogenic risk), and carcinogenic Risk (CR) indices. The average concentrations of the Pb and Cd were significantly ($P < 0.05$) lower than the safety limit in all seasons for three years. However, 2.3% of Pb in the total samples exceeded the European Commission and FAO/WHO standards. All estimated values for non-carcinogenic risk were in the safe range (HQ < 1) among all consumers. The mean value of total CR for Pb was 1.23×10^{-6}, 1.75×10^{-6}, and 8.03×10^{-7} for adult, children, and Arab populations, respectively**.** For Cd exposure, the total CR value was 2.2×10^{-4}, 3.13×10^{-4} and 1.44×10^{-4} for adult, children, and Arab populations, respectively. Cancer risk values determined for Cd were generally in the unsafe range during three years, indicating that there was CR for all consumers by ingestion intake of Cd contained in wheat flour in this study area. The results obtained indicated that the government requires implementing more remediation or intervention to control and mitigate the contamination burden of Cd in agricultural crops to reduce its associated carcinogenic risks.

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INTRODUCTION

Heavy metals from lactogenic and anthropogenic sources are ubiquitous in the environment and their elevated concentration is the greatest threat to human health because of their toxicity, bioaccumulation, bio-magnification, and persistence in the food chain [1]. The accumulation of potentially toxic heavy metals including chromium (Cr), arsenic (As), mercury (Hg), cadmium (Cd), and lead (Pb) can cause acute and chronic effects on human health even at a low concentration such as type of cancer [2, 3], renal tubular damage [4, 5], osteoporosis [6], delay in the development of mental and physical tissues in children [7], kidney issues, and high blood pressure [5, 8]. Atmospheric deposition, vehicular exhaust, waste disposal, application of sewage sludge, use of pesticides, and fertilization in arable land increase the concentration of heavy metals in soil and agricultural crops [7, 9].

Heavy metal contamination of agricultural crops may pose the greatest problem for human health in a long time. It was evidenced that dietary intake through contaminated food is the primary pathway of human exposure to heavy metals (> 90% of exposure) compared with other routes, such as dermal contact and inhalation [1, 2]. In this context, Food and Agriculture Organization (FAO) and World Health Organization (WHO) [10, 11], and European Commission (EC)[12, 13] strictly regulated the maximum or allowable permitted concentrations of toxic heavy metals in foodstuffs. Therefore, the evaluation of potential health risk in agricultural crops and foodstuffs are essential to protect human health. The health risk assessment associated with the daily intake of toxic metals is the systematic process to estimate the effect of potential carcinogenic and non-carcinogenic risk on human health for a certain time frame [2, 14]. United States Environmental Protection Agency (US EPA) established this model and it has been widely implemented to examine health risk of various foodstuffs [14].

Common wheat (*Triticum Aestivum L.*), also known as bread wheat, is the most important agricultural crop worldwide and has a significant contribution to human diet with a global production of 735.9 million tons in 2018/2019 [15, 16]. In 2015, the average worldwide per-capita consumption was 68 kg and it was 95 kg and 61 kg in developed and developing countries, respectively [17].

Iran is well known as the second-largest wheat user in the Middle East and the first- largest wheat producer in Near East Asia with high rate exportation to Arabic countries such as Bahrain, Kuwait, Lebanon, Oman, Qatar, and United Arab Emirates [18, 19]. According to recent data published by FAO, Iranian's annual wheat consumption on average consumes is 2.5 times (167.6 kilograms per year) more than that of the global average (67.1 kg) [20]. Likewise, It was reported that 41.8 million tones of wheat are produced in Near East Asia total, with 21 million tones in Turkey, 14.5 million in Iran, 8.6 million in Egypt, 3.8 million in Iraq, and 2.4 million in Syria [19]. Since wheat flour is an essential ingredient for population and it constitutes by 50–60% of the food requirement for Iranian and international consumers [15, 17]. Thus, assessment of potential risks via wheat flours consumption in Iran is essential to evaluate food safety [18, 19]. Although wheat flour is a critical foodstuff in Iran, there is no published information concerning the health risk (non-carcinogenic and carcinogenic or cancer risk) of heavy metals uptake via the wheat flours consumption.

Abouiyan Jahromi et al. (2018) reported that the concentration of Cd, Zn, and Pb in agricultural lands around Irankouh mine (it was located in Isfahan, Iran) were significantly higher than the permissible limits in soil that are set by the Iranian National Standard Organization and Food and Agriculture Organization/World Health Organization[21]. They indicated that higher concentrations of Cd, Zn, and Pb in agricultural lands were affected by mining activities. Amir Hossein Baghaie et al., (2019) examined the level of contamination of Cd and Pb in soil and wheat in Shazand County, central of Iran. The carcinogenic risks of Pb via wheat consumption was higher than 1×10^{-6}[21]. A study in Iran assessed the concentrations of Cd, Pb, Fe, and Ni in soils, rice, onion, and wheat grown in agricultural lands in Isfahan province, central Iran[22].

They indicated that the average concentration of Pb, Cd, and Ni in the crops and soil exceeded the permissible limits provided by the USEPA and FAO/WHO standards. Likewise, they reported these agricultural lands in this area are at a serious health risk because the values obtained from the target hazard quotient were more than one. We hypothesized that fertilizer application particularly at high concentration would increase the accumulation and rate of heavy metals in wheat grain and therefore lead to high health risk for human consumption. Assessment of human health risk is an effective approach that widely used to examine the risk of heavy metals and others pollutants via ingestion and dermal pathways. In such an evaluation, several indices (threshold hazard quotient, hazard index, and threshold carcinogenic risk) are widely used to examine the level of non-carcinogenic and carcinogenic risks of heavy metals in food materials on human health.

Notable, large agricultural lands in Iran fall within semi-arid regions. Therefore, only about 25% of the cultivated land is rained, and about 85 % of the total agricultural lands are irrigated [18, 23]. In the recent decade, due to the limitation in availability of freshwater for irrigation, most of the total cultivated regions are irrigated by dam water and treated wastewater especially sewage [18]. Although, reuse of sewage wastewater and dam water can be beneficial for irrigation in agricultural lands as a rich source of important nutrients and minerals, there are health burdens that have been considered to prevent accumulation of toxic compounds such as heavy metals [24]. Thus, a regular assessment of heavy metals and their health risk is essential to better understand possible harmful effects on food safety [1, 14]. With regard to this fact, we aimed to assess contamination of selected toxic heavy metals in wheat flour for commercial brands in Iran and examine potential health risk for national (adults and children) and international (Arab population) inhabitants that exposed to heavy metals through consumption of wheat flour.

MATERIALS AND METHODS

Sample collection and preparation

A total of 335 wheat flours samples (<0.25 mm) of four commercial brands have been collected during 2016 to 2018 from Khouzestan province, Iran. Khouzestan province has been produced 535,000 tons of wheat, which was the first producer of wheat in Iran [29]. We used the factorial method to estimate the sample size based on considering 4 main commercial brands in Iran, 2 heavy metals, 4 seasons, 3-study population, and 3 repetitions. Based on the factorial model, the sample size was equal to 288 samples. However, in this study, for more accuracy, 335 samples were randomly purchased from the market and analyzed as the final sample size.

At the same time, flour samples were homogenized and stored in tightly closed plastic bags at a cool place (4°C) until analysis. In the laboratory, we used the Official Methods of Analysis (AOAC, 2003) for sample preparation. 10 g of flour samples were thoroughly oven-dried at 100 C to remove the moisture and stored at − 20°C [25].

Reagents and Laboratory Analysis

In this study, we used reagent-grade chemicals and ultrapure water to make all solutions. Likewise, we purchased internal standard containing, multi-element standard, standard stock, and mixture acid solutions from Merck (Darmstadt, Germany). A microwave digestion method (milestone microwave, USA) was also implemented to extract dried samples based on EPA procedure 3050B [26]. About 0.5 g of dried samples was digested at 200°C using a mixture solution (HNO_3 and HClO4, 5:10) during 30–40 min. After cooling, we used Milli-Q water to adjust the total volume of digested samples to 25 mL. Then, all samples were filtered by syringe filter (pore size = 0.45 mm, DISMIC®- 25HP PTFE).

Instrumental analysis and quality control analysis

Determination of heavy metals was performed with Graphite Furnace Atomic Absorption Spectrometry (GFAAS; Varian 240FS AA). It was equipped with Deuterium light and auto-sampler [27]. For each analytical batch, a run included an internal standard, reagent blank, a sample replicate (three times), and representative reference standard to confirm accuracy and efficacy of the analytical data. We estimated detection limits for all variables using a standard procedure. Likewise, the relative standard deviation (RSD) was estimated to clarify the repeatability and rep-reducibility of the applied method. In this study, the percentages of RSD were acceptable (below 5%) for the applied method. Two standard reference materials (SRM) of the plant were used to examine the instrument variability and quality control. The SRM of the plant included rice flour (804 IRMM) supplied from the European Commission, Institute for Reference Materials and Measurement. The percentages of recovery of Pb (89%) and Cd (101%) were acceptable, which confirmed the accuracy and precision of the analytical procedure.

Health risk assessment

We implemented the human health risk assessment (HHRA) model in this study to detect the potential risk of Cd and Pb via ingestion intake of wheat flour in Iran[2, 14]. Since Iran is the first- largest wheat producer in Near East Asia with a high rate of exportation to Arabic countries, the risk model in this study was assessed for both national (Iranian adult and children) and international consumers (Arab population). This HHRA model was recommended by the US EPA to assess essential requirements of health risk including CDI, THQ, HI and TCR (Table 1) [14].

Table 1. Parameters of health risk assessment models

Factor	Definition	Unit	Value			Reference
			Adult	Child	Arab	
CDI	Chronic daily intake	mg Kg^{-1} day				[2]
C	Concentration of elements in Wheat flour	mg Kg^{-1}				
IR_d	Average Consumption rate of wheat flour	g day^{-1}	167.6	55.7	109	[20]
BW	Average body weight	Kg	70	16.2	70	[28]
ED	Exposure duration	Years	30	6	30	[2, 14]
EF	Exposure frequency	Days per year	350			
AT	Average time	Days	365×ED[a] 365× 74.8[b]			[2]
HQ	Hazard Quotient					[28]
RfD	Oral reference dose	mg Kg^{-1} day	Cd: 0.001, Pb: 0.004			[2]
HI	Hazard index					[28]
CSF	Cancer slope factor	mg Kg^{-1} d	Cd: 15, Pb: 0.0085			[29], CALEPA [c]

[a] Non-carcinogenic risk; [b] Cancer risk, [c] California Environmental Protection Agency, U.S

Exposure assessment

Chronic daily intake (CDI) is estimated to examine exposure dose to heavy metals through direct ingestion routes [28]. In this study, we compared CDI value with the respective tolerable daily intake (TDI) [30], and provisional tolerable daily intake (PTDI) [30]. Equation 1 was used to estimate CDI values which are adapted from US EPA [2, 14]:

$$CDI = (C\times EF \times IR_d \times ED) / AT \times BW) \times 10^{-6} \quad (1)$$

Non-carcinogenic risks

The Hazard Quotient (HQ) is a non-carcinogenic risk that is calculated by using the ratio between the CDI and oral reference dose (RfD) of each heavy metal. The RFD was defined as "an estimation of the daily exposure to which the human population could be continually exposed over a lifetime without an appreciable risk of deleterious effects" [28]. If the HQ for individual elements exceed the unity (considered as 1), it is assumed that potential non-carcinogenic effects and unsafe conditions on the exposed population [2].

Likewise, we estimated the hazard index (HI) to assess total potential non-carcinogenic risks for both heavy metals [2, 14].

$$THQ= CDI / RfD \qquad (2)$$

$$\text{Total THQ (HI)}= \sum THQ \qquad (3)$$

Carcinogenic risks

EPA defines carcinogenic risks (CR) as “the incremental probability of an individual to develop cancer, over a lifetime, as a result of exposure to a potential carcinogen”[2]. In this study, the carcinogenic risks were estimated based on the equation 4. International Commission on Radiological Protection (ICRP) considered a risk level of “5.0×10^{-5}” as the maximum acceptable level of carcinogenic risk for chemical carcinogens. But, the acceptable level of cancer risk recommended by USEPA ranges from 10^{-6} to 10^{-4}. This means the level of 10^{-4} consider as the point of excess for CR [14, 28].

$$CR= CDI \times CSF \qquad (4)$$

Data analysis

We used statistical software SPSS 16 (SPSS, Chicago, IL) and Excels in this study to analyze data. Descriptive statistics were used to estimate the mean, coefficients of variation, and standard division of the heavy metals and health risk indices in wheat samples. We also used a one-way analysis of variance (ANOVA) to estimate significant changes of elements in different groups. The significant difference level was considered at $P < 0.05$.

RESULTS AND DISCUSSION

Heavy metals content in wheat flour

In this study, we initially selected European Commission and Food [12] and FAO/WHO guideline [11] as the evaluation criterion for Pb and Cd because the permissible limits of heavy metals are stricter in these standards. A total of 335 wheat flour samples were analyzed to estimate the concentrations of Pb and Cd in different seasons from 2016-2018 in Khuzestan, Iran. All data were summarized in Table 2. The average concentrations of the entire test Pb (0.063±0.35) and Cd (0.015±0.011) were significantly ($P < 0.05$) lower than the corresponding safety limit presented in the European Commission and FAO/WHO standards in all seasons during three years. This result suggests that heavy metals concentration in wheat flour was within a safe threshold; therefore, the irrigated regions in Khuzestan may still safe for the cultivation of the wheat crop. The finding of this result is in agreement with another study in Khuzestan that reported 76% of the irrigated regions in Khuzestan is unpolluted and the level of heavy metals in farmland soils lower than the thresholds set by the environmental quality standards for agriculture activity [31, 32].

Compared with those surveys conducted in Iran and other countries, the average concentration of Pb and Cd in the present study was lower than those observed in Kanpur (India) [33], Noyelles-Godault (France)[34], Kunshan and Jinghui (China) [35], Hamedan and Tehran (Iran) [36, 37]; and were higher to those in Turkey and Edirne [38], Tianjin (China) [39], Bushehr and Golestan provinces in Iran [40].

A notable, cumulative effect of Pb in this area was observed. Our finding showed that 11 % and 2.3% of Pb in the wheat flour samples exceeded these standards in summer and autumn, respectively. The highest concentration of Pb (0.55 mg Kg^{-1}) in wheat flour was ~2.3 times more than the European Commission standard value (0.24 mg Kg^{-1}) and 1.67 times of the FAO/WHO standards (0.430 mg Kg^{-1}) (Table 2), which shows the high level of Pb concentration in some wheat flour samples. This probably results from different soil quality of the irrigated region, capabilities of accumulation, and absorption of heavy metals. This result is consistent with the study on heavy metals contamination in farmland soil in Khuzestan by Ahmadi et al. (2017). They reported that the concentration of As, Cd, and Pb were higher than the environmental standards in 24% of farmland in Khuzestan, Iran [31, 41].

Likewise, the descriptive statistics showed that Pb and Cd varied with the coefficients of variation (CV) that ranged from 42 to 76.2 % that showed considerable variability of heavy metals in wheat flour samples (Table 2). Therefore, the temporal distributions of Pb and Cd in this area were non-homogeneous. This significant variation of heavy metal content could be due to seasonal fluctuations during the long period of sampling [9, 24]. However, more studies reported that the chemical properties of farmland soil and agriculture products are also significantly associated with atmospheric deposition and pollution load from anthropogenic sources (e.g., river discharge, chemical fertilizers, and pesticides)[25, 31]. These environmental factors can cause significant variation in bioavailability, enrichment and mobility of heavy metals during temporal scales [25, 32].

Table 2. Heavy metals concentration in wheat flour

Heavy metals	Seasons	n	Heavy Metals Concentration (mg Kg^{-1})			Mean	Range	CV [a] (%)	Percent Exceeded Standards (%)
			2016	2017	2018				
Pb	Spring	79	0.050±0.033	0.068±0.056	0.035±0.025	0.051±0.035	0.010-0.220	0.68	0
	Summer	111	0.071±0.0105	0.077±0.067	0.50±0.032	0.066±0.052	0.06-0.500	0.76	11 [b](n =5)
	Autumn	81	0.029± 0.041	0.087±0.083	0.068±0.043	0.061±0.044	0.004-0.245	0.72	2.3 (n =2)
	Winter	64	0.059±0.072	0.070±0.049	0.067±0.039	0.065±0.033	0.06-160	0.51	0
Average			0.052±0.055	0.075±0.064	0.055±0.035	0.0633±0.35	0.052-0.075	0.55	0
Cd	Spring	79	0.011± 0.064	0.016±0.08	0.010± 0.007	0.012±0.051	0.002-0.030	0.42	0
	Summer	111	0.023± 0.02	0.020±0.015	0.015±0.005	0.019±0.016	0.005-0.110	0.84	0
	Autumn	81	0.013±0.09	0.022±0.014	0.011±0.002	0.015±0.009	0.001-0.060	0.60	0
	Winter	64	0.015±0.010	0.013±0.014	0.018±0.007	0.017±0.009	0.003-0.060	0.56	0
Average			0.015 ±0.014	0.018±0.012	0.013± 0.006	0.015±0.011	0.013-0.018	0.75	0

[a] coefficients of variation; n, Number of samples: ± Standard deviation; [b] Values in the parenthesis is the number of samples which concentrations of heavy metals exceeded values or permissible limits of European Commission (pb and Cd: 0.24 mg/) and Food and Agriculture Organization and World Health Organization (FAO/WHO) (Pb: 0.430 and Cd: 0.21).

Human health risk assessment

Both carcinogenic and non-carcinogenic risk assessment of Pb and Cd were conducted in this study for national (Iranian child and adult) and international consumers. The health risk approach is a practical model to assess “the food safety quality in terms of dietary exposure, bioactive contaminants, and identifying potential exposure to food contaminants” [2, 14]. For all populations, the CDI values of Cd and Pb from wheat flour consumption in this study were below TDI and PTDI levels (Table 3), suggesting that the daily intake level of Pb and Cd from the wheat flour ingestion was below the level of concern. The HI and HQ levels from the wheat flour ingestion for international and Iranian consumers were also summarized in Table 4 and Figure 1. As data are shown for all consumers, HQ and HI values never exceeded the threshold of 1. This indicated that all national and international consumers in Khuzestan might be exposed to significant non-carcinogenic effects during their lifetime that are associated with consumption of the wheat flour. Likewise, our results showed that the total HI of Pb and Cd in the children population was approximately 1.7 and 2.1 times more than adults and Arab populations, respectively (Figure 1). Therefore, children were more sensitive to heavy metals exposure than adults in this area through the consumption of local wheat flour. This is consistent with several studies that reported that children are more exposed to environmental toxicants than adults because they are constantly growing and drink more water, breathe more air, consume more food in proportion to their weight [4, 42]. Likewise, children's immune, central nervous, digestive, and reproductive systems are not well developed physically. Therefore, exposure to contaminated air, food, and water at certain early stages of development can lead to irreversible damage [4, 7, 10].

Table 3. Estimated chronic daily intake (CDI) of heavy metals by consuming wheat flour by national and international consumers

		CDI *(mg Kg^{-1} day) (n=335)*											
	Years	**2016**			**2017**			**2018**			**Average 3 years**		
	Seasons	Adult	Child	Arab	Adult	Child	Arab	Adult	Child	Arab	Adult	Child	Arab
Pb	**Spring**	1.19E-04	1.69E-04	7.76E-05	1.56E-04	2.22E-04	1.02E-04	8.05E-05	1.14E-04	5.25E-05	1.17E-04	1.67E-04	7.66E-05
	Summer	1.65E-04	2.34E-04	1.07E-04	1.76E-04	2.51E-04	1.15E-04	1.15E-04	1.63E-04	7.48E-05	1.51E-04	2.16E-04	9.88E-05
	Autumn	6.72E-05	9.56E-05	4.39E-05	2.00E-04	2.84E-04	1.30E-04	1.57E-04	2.23E-04	1.02E-04	1.41E-04	2.01E-04	9.21E-05
	Winter	1.36E-04	1.93E-04	8.86E-05	1.61E-04	2.29E-04	1.05E-04	1.55E-04	2.20E-04	1.01E-04	1.51E-04	2.15E-04	9.85E-05
Average		1.21E-04	1.72E-04	7.90E-05	1.73E-04	2.47E-04	1.13E-04	1.26E-04	1.80E-04	8.24E-05	1.45E-04	2.06E-04	9.45E-05
Cd	**Spring**	2.55E-05	3.63E-05	1.67E-05	3.80E-05	5.40E-05	2.48E-05	2.33E-05	3.31E-05	1.52E-05	2.82E-05	4.01E-05	1.84E-05
	Summer	5.39E-05	7.66E-05	3.51E-05	4.58E-05	6.52E-05	2.99E-05	3.46E-05	4.92E-05	2.26E-05	4.46E-05	6.35E-05	2.91E-05
	Autumn	2.99E-05	4.26E-05	1.95E-05	5.20E-05	7.40E-05	3.39E-05	2.54E-05	3.62E-05	1.66E-05	3.44E-05	4.89E-05	2.24E-05
	Winter	3.45E-05	4.90E-05	2.25E-05	2.98E-05	4.24E-05	1.95E-05	4.30E-05	6.12E-05	2.81E-05	3.96E-05	5.63E-05	2.58E-05
Average		3.59E-05	5.11E-05	2.34E-05	4.21E-05	5.99E-05	2.75E-05	3.02E-05	4.30E-05	1.97E-05	3.61E-05	5.14E-05	2.36E-05

All CDI values were lower than Provisional tolerable daily intake values (in mg BW per day) of heavy metals (Pb: 0.00357and Cd: 0.00066) and Maximum tolerable daily intake (Pb: 0.003 and Cd: 0.0008)

Table 4. Target hazard quotient (THQ from Wheat flour consumption by national and international consumers

		HQ of heavy metals (n=335)											
	Years	**2016**			**2017**			**2018**			**Average 3 years**		
	Seasons	Adult	Child	Arab	Adult	Child	Arab	Adult	Child	Arab	Adult	Child	Arab
Pb	**Spring**	0.030	0.042	0.019	0.039	0.055	0.025	0.020	0.029	0.013	0.029	0.042	0.019
	Summer	0.041	0.059	0.027	0.044	0.063	0.029	0.029	0.041	0.019	0.038	0.054	0.025
	Autumn	0.017	0.024	0.011	0.050	0.071	0.033	0.039	0.056	0.026	0.035	0.050	0.023
	Winter	0.034	0.048	0.022	0.040	0.057	0.026	0.039	0.055	0.025	0.038	0.054	0.025
Average		0.030	0.043	0.020	0.043	0.062	0.028	0.032	0.045	0.021	0.036	0.052	0.024
Cd	**Spring**	0.026	0.036	0.017	0.038	0.054	0.025	0.023	0.033	0.015	0.028	0.040	0.018
	Summer	0.054	0.077	0.035	0.046	0.065	0.030	0.035	0.049	0.023	0.045	0.063	0.029
	Autumn	0.030	0.043	0.020	0.052	0.074	0.034	0.025	0.036	0.017	0.034	0.049	0.022
	Winter	0.034	0.049	0.022	0.030	0.042	0.019	0.043	0.061	0.028	0.040	0.056	0.026
Average		0.036	0.051	0.023	0.042	0.060	0.027	0.030	0.043	0.020	0.036	0.051	0.024

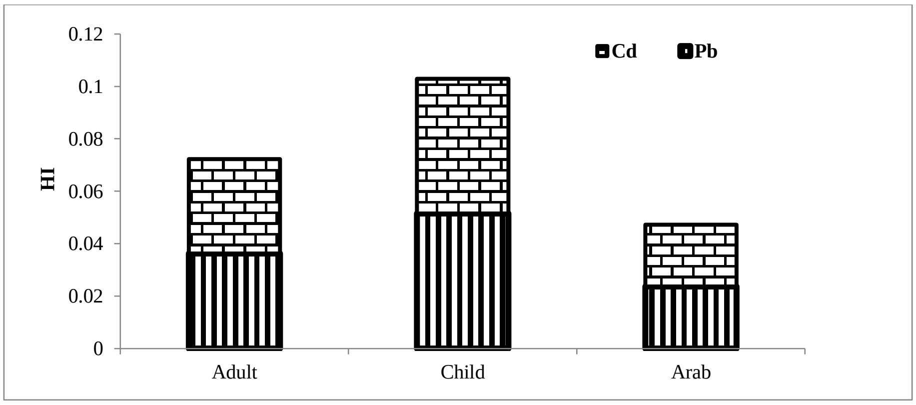

Figure 1. Contributions of heavy metals to non-carcinogenic risk (HI) from wheat flour consumption

Table 5. carcinogenic risk (CR) from wheat flour consumption by national and international consumers

	Years	2016			2017			2018			Average 3 years		
	Seasons	Adult	Child	Arab	Adult	Child	Arab	Adult	Child	Arab	Adult	Child	Arab
Pb	**Spring**	9.01E-05	1.44E-06	6.60E-07	1.32E-06	1.88E-06	8.64E-07	6.84E-07	9.73E-07	4.46E-07	9.97E-07	1.42E-06	6.51E-07
	Summer	1.40E-06	1.99E-06	9.13E-07	1.50E-06	2.13E-06	9.79E-07	9.74E-07	1.39E-06	6.36E-07	1.29E-06	1.83E-06	8.40E-07
	Autumn	5.71E-07	8.13E-07	3.73E-07	1.70E-06	2.41E-06	9.11E-05	1.33E-06	1.89E-06	8.68E-07	1.20E-06	1.71E-06	7.82E-07
	Winter	9.15E-05	1.64E-06	7.53E-07	1.37E-06	1.95E-06	8.94E-07	1.32E-06	1.87E-06	8.58E-07	1.28E-06	1.82E-06	8.37E-07
Average		1.03E-06	1.46E-06	6.71E-07	1.47E-06	2.10E-06	9.62E-07	1.07E-06	1.53E-06	7.01E-07	1.23E-06	1.75E-06	8.03E-07
Cd	**Spring**	1.56E-04	2.22E-04	1.02E-04	2.32E-04	3.29E-04	1.51E-04	1.42E-04	2.02E-04	9.27E-05	1.72E-04	2.45E-04	1.12E-04
	Summer	3.28E-04	4.67E-04	2.14E-04	2.80E-04	3.98E-04	1.82E-04	2.11E-04	3.00E-04	1.38E-04	2.72E-04	3.87E-04	1.78E-04
	Autumn	1.83E-04	2.60E-04	1.19E-04	3.17E-04	4.51E-04	2.07E-04	1.55E-04	2.21E-04	1.01E-04	2.10E-04	2.98E-04	1.37E-04
	Winter	2.10E-04	2.99E-04	1.37E-04	1.82E-04	2.59E-04	1.19E-04	2.62E-04	3.73E-04	1.71E-04	2.41E-04	3.43E-04	1.57E-04
Average		2.19E-04	3.12E-04	1.43E-04	2.57E-04	3.65E-04	1.68E-04	1.84E-04	2.63E-04	1.20E-04	2.20E-04	3.13E-04	1.44E-04

CR of heavy metals (n=335)

* Red color shows High risk (unsafe level), yellow color is border-line and green color shows safe level of CR

The mean values of CR for Pb due to wheat flour consumption were 1.23×10^{-6}, 1.75×10^{-6}, and 8.03×10^{-7} for adult, children and Arab populations, respectively (Table 5). Thus, the CR values for Pb in three years were generally in a safe range (Pb<10^{-4}), suggesting that there was no cancer risk for both consumers by ingestion of Pb contained in wheat flour in this study area. For Cd, the total CR values in this area exceeded the USEPA and ICRP risk management limits for all consumers. The average total CR for Cd was 2.2×10^{-4}, 3.13×10^{-4} and, 1.44×10^{-4} for adult, children and Arab populations, respectively. These values were 1.44 to 3.13 times more than the USEPA and ICRP safe limit, respectively.

Although the heavy metals concentration in wheat flour was in the safe limit of standards, a potential CRs for a human could still be high, particularly for Cd, which accounted for about 80 to 90% of the total CR. Chemical pesticides and fertilizers contain several types of heavy metals [34, 39], which are the main sources of heavy metals in agriculture products [43]. The Cd concentration in fertilizer was ranged from 0.1 to 11.4 mg Kg^{-1}. Likewise, insecticides and herbicides are causing accumulation of Cd in agriculture products [31, 43]. This could be related to the competition between Ca^{2+} and Cd^{2+} during plant uptake in farmlands. More studies showed that Cd^{2+} simply replaces Ca^{2+} due to the similarity in the valence of the two ions and the ionic radius [27, 43]. Therefore, it seems that Cd has a major contribution in developing the CR in this area [42-44]. However, the Iranian standards provide a limit for the heavy metals concentrations [31]. Our finding is in agreement with the evaluation conducted in Hamedan, Iran [36, 37]. They indicated that the possibility of increasing CR from heavy metals via wheat consumption ranged from 1.07×10^{-4} to 3.2×10^{-4}, which was an unsafe CR risk level for national and international consumers. Our finding is also in accordance with the studies done in Jinghui, Kushan, and Zhejiang, in China [35, 43], and Boolaroo (Australia).

Uncertainty of risk

It should be pointed out that there is some uncertainty associated in health risk assessment that could not be determined and may limit the validity of the results. For example, (i) the effect of Pb and Cd toxicity may be different for an individual, (ii) daily intake of wheat flour for children were acquired not estimated, (iii) most of the probability distribution derived from USEPA data used for health risk simulation, (iv) the oral cancer slope factor was constant for all consumers, but in reality, it could be varied for a different person of the population, and (v) the risk in this study was only estimated based on the Pb and Cd toxicity, but the fact is that other possible exposure pathways can affect wheat flour content such as organochlorines and polyaromatic hydrocarbons (PAHs). Therefore, the cumulative health risk of all chemical elements from ingestion intake of wheat flour may be higher than that estimated levels. Therefore, policymakers and environmental managers would be better considered these uncertainties in decision making. Although, our finding in this study may not provide an entirely accurate scenario of potential health risk, we tried to conduct a primary study on human health hazards of heavy metals to national and international consumers in Khuzestan, Iran.

CONCLUSIONS

All of the mean concentrations of Pb and Cd in wheat flour obtained from the irrigated area of Khuzestan were below the maximum allowable level recommended by the international standards, and Pb exceeded the safety thresholds of these standards in 15% of the flour samples. The non-carcinogenic risk through wheat flour consumption for heavy metals and combined metals were not observed in the study area. Although the heavy metals concentration in wheat flour were lower than the safe limit of standards, the potential carcinogenic risk for human was high, and Cd poses a CR for both national and international consumers. The combined results of individual consumers indicated that carcinogenic and non-carcinogenic risks of Pb, in wheat flour products are safe for all consumers. For Cd exposure, the government requires to implement more remediation or intervention to control and mitigate the contamination burden of Cd in agricultural crops and soil to reduce its associated carcinogenic risks.

Abbreviation

THQ: Target Hazard Quotient; HI: Hazard Index; RFD: Reference Dose; ADD: Average Daily Dose; IR: Ingestion Rate; BW: Body weight; ED: Exposure duration; EF: Exposure Frequency: AT: Averaging Time; CF: Conversion Factor; SA: Skin Surface; US EPA: United State Environmental Protection Agency; HHRA: Human Health Risk Assessment; LOD: limit of detection; EC: Electrical Conductivity; IARC: Agency for Research on Cancer, WHO: World Health organization; TCR: Total Carcinogenic Risk; HQ: Hazard Quotients

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Availability of data and materials

The datasets generated and analyzed during this study are included in the main document of this manuscript.

Authors' contributions

BZGO involved in writing up of the research proposal, performed sampling and laboratory analysis, presented the results, and is the corresponding author. HA initiated the research concept, interpreted results, and finalized the manuscript document. SBTS presented the results and discussions, interpreted results, wrote up of the draft manuscript. MT and HSH performed laboratory analysis and analyzed the data. MF analyzed the data and involved in manuscript reviewing.

ETHICAL CONSIDERATION

We obtained ethical clearance from the Ahvaz Jundishapur University of Medical (IR.AJUMS.REC.1397.607).

Consent for publication

Not applicable

Conflict of interests

The authors declare that they have no competing interests.

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