JCHR (2024) 14(4), 795-810-0

Journal of Chemical Health Risks

sanad.iau.ir/journal/jchr

ORIGINAL ARTICLE

Determination of Arsenic and Trace Elements Exposure in Commercial Fishes on the Iran Market: Health Risk Assessment

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(Received: 17 June 2023 Accepted: 15 October 2024)

KEYWORDS

Heavy metals;
Environmental pollution;
Health risk assessment;
Public pealth,
Food safety

ABSTRACT: Consuming food contaminated with toxic heavy metals is a main exposure rout of these substances entering the human body and is a serious threat to the health of communities. The present study aimed to estimate human health risk when exposed to arsenic and heavy metals due to the consumption of commercial fish in Iranian market. Nine species of commercial fishes were supplied from the public market in the city of Mashhad, Iran. Ninety samples were randomly selected from nine each species, and then concentration of heavy metals was measured. The concentration of heavy metals was measured with an inductively coupled plasma emission spectrometer. The health risk assessment-based EPA model was used to explore carcinogenic and non-carcinogenic risks. Hazard Quotient (THQ) in all species was less than 1 for adults, but the hazard index of all species was higher than 1, with a mean value of 2.09 ± 0.33 ranging between 1.3 and 2.86. The hazard quotient for children was higher than 1 in two metals, lead, and zinc. The hazard index for all was higher than 1, with a mean value of 6.39 ± 1.60 ranging between 4.21 and 8.77. Cancer risk (CR) assessment showed that in adults, the three metals arsenic, cadmium, and lead were within the safe range (CR $\geq 1\times10^{-4}$) and only chromium was in the borderline of CR. Among children, the CR for cadmium and lead was in the safe range (CR $\geq 1\times10^{-4}$) and for arsenic and chromium was in the borderline. There are potential carcinogenic and non-carcinogenic risks associated with consuming the fish commonly sold in Iranian market. The presence of heavy metals in aquatic products consumed in Mashhad can affect consumers' health. The results of this monitoring can facilitate health decision-making and improve human health.

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(A. Afshari; F. Behyad; S. B. Tavakoly Sany)
DOI: 10.60829/jchr.2024.6171760

INTRODUCTION

Food security is a major concern in human societies. With the progress of science and knowledge, many infectious diseases that threatened people's health in the past were controlled and eradicated [1]. Currently, the spread of non-communicable diseases such as obesity, diabetes, cardiovascular diseases and different types of cancer is the major concern in human communities worldwide. It is a health priority to prevent these diseases on a large scale in institutions active in health domain in the world [2]. Following a healthy diet is considered a main factor positively affecting the prevention of the above-mentioned diseases. Aquatic food, especially fish and shrimp, is a major source of protein in human nutrition. The demand and supply of aquatic food is on the rise; thus, it is expected to be free from chemical pollutants [3, 4].

Currently, aquatic animals are a major source of human food in the country. About 21% of the world's animal protein comes from fish and birds [4-6]. The use of aquatic food stuff, especially fish, as a source of protein, has increased with the growing population and stronger needs for food [7]. Unfortunately, the rapid growth of population and residential, commercial, industrial and agricultural centers increased urban, industrial and agricultural waste and sewage every year and further polluted the environment for humans and aquatic organisms [5]. Persistent chemical pollutants such as heavy metals are among the major pollutants of Iran’s water supplies. Due to their high toxicity, these compounds are known as the main pollutants in the whole world. These compounds have different properties such as toxicity, mutagenicity, carcinogenicity and estrogenicity [5, 8].

Contamination of food supplies by heavy metals is a major threat to human health [9]. So far, different diseases have been reported to be induced by accumulated heavy metals in fish and the adverse effects on aquaculture production. There is research evidence that lead causes kidney failure, liver damage, coma, mental retardation, and even death. Although copper, iron, manganese and zinc are essential elements for metabolism, when their concentrations accumulate at certain thresholds, they will have significant health risks [4-6]. Relatively high levels of copper and zinc can cause nephritis, anuria and damages to kidney. For its effects on cellular defense and energy production, mercury causes widespread toxicity in many organs such as the nervous system, cardiovascular system, and digestive system. Research also suggests that cadmium can damage the kidneys, cause acute hypocalcemia and reduce growth [10, 11].

Long-term exposure to these substances can damage several organs in the body, such as the brain, lungs, liver, and kidneys. In several studies, the high toxicity of heavy metals such as mercury, lead and cadmium has been proven in fish. Therefore, if the permissible amount of these metals in the edible tissue of fish increases, many problems can rise for health in society [4-6]. Estimating the concentration of heavy metals in the edible tissue of aquatic animals helps to find whether they are present or not. Their accurate level can be measured along with the high level beyond the standard limit. The current research provides insightful remarks on the presence of heavy metals in human food, which can threaten food security and public health in society [10, 11].

The risk assessment model was developed by the US Environmental Protection Agency to estimate the potential risk of pollutants for human health. Risk assessment is defined as the identification and quantification of the risks of consuming a specific chemical substance. In doing so, the potential adverse effects of the chemical are considered if consumed at the recommended amount or more if exposed in any possible way [12, 13]. As defined by the World Health Organization (WHO) and the International Chemical Safety Program, risk assessment serves to estimate the present and future negative health effects when an organism, system or population is exposed to environmental chemical pollutants [5, 6].

Consuming food contaminated with heavy metals is a main way of these substances entering the body and getting gradual accumulated. If the concentration of these metals in food is higher than the permissible limit, they can be considered a serious threat to the health of society [2]. In-depth research is needed to provide comprehensive information about the concentration of heavy metals, daily intake rate of these substances and the hazard quotient. The resultant information contributes to health domain, food security, development of health programs and improvement of health indices. The present research has nutritional and health implications as the ultimate goal is to prevent human suffering caused by different diseases and the complications of consuming aquatic animals contaminated with heavy metals [14, 15]. The present research aimed to estimate the concentration of arsenic and heavy metals (chromium, lead, mercury, cadmium, copper, nickel, arsenic, zinc, copper, manganese and cobalt) in the muscle tissue of commercial fish sold in Iranian market. It also estimated the human health risk (carcinogenic and non-carcinogenic risks) when exposed to arsenic and heavy metals by consuming commercial fish sold in the national market.

MATERIALS AND METHODS

As reported by the Fisheries and Aquatics Affairs of Khorasan Razavi Agricultural Jihad Organization, about 9 types of aquatics are widely demanded and consumed in the city of Mashhad. These include the fish transported from the South Sea (mackerel, sciaenidae, silver pomfret and Indo-pacific king mackerel), the Caspian Sea (Caspian kutum and mullet) and farmed fish (trout and salmon). To measure the concentration of heavy metals (chromium, lead, mercury, cadmium, copper, nickel, arsenic, zinc, copper, manganese and cobalt), samples were taken from the muscle tissues of the 9 species. The samples were purchased at the local market (of Mashhad) in 2022, and 10 samples were taken from each species randomly, which made 90 samples overall. Upon delivery at the laboratory, the samples were kept in a cold room at minus 20 degrees of Celsius until they were prepared for analysis. The preparation included a process of digestion, separation and purification, all done according to the guidelines by the Environmental Research Institute [5, 9].

Lab analyses

The outer surface of the fish body was washed with distilled water and the target tissue (muscle) was separated. The samples were dried using a freeze dryer at -40 degrees of Celsius for 8-10 hours and were powdered with a porcelain mortar. In the digestion step, first, 0.5 grams of the powdered sample were weighed using a TE313J scale with an accuracy of 0.001 grams. To the weighed samples, 7 ml of 65% concentrated nitric acid and 1 ml 30% hydrogen peroxide was added. Then, the samples were transferred to a microwave device (ETHOS). After the digestion when the samples turned into the mineral phase, to estimate the concentration of elements, inductively coupled plasma (ICP) spectrometer was used. The detection limit of the ICP spectrometer is shown in Table 2 for different elements. So is the wavelength of the ICP spectrometer to measure heavy metals.

Quality control

The glass containers and plastic bottles used during the analysis were washed in nitric acid solution for 24 hours and rinsed using deionized water. Then the bottles were dried at room temperature and sealed. The detection limit of the sampling instrument was estimated through a standard method (Table 1). To control the quality of all heavy metal samples, in addition to replicating the test three times for each element, the calibration graphs of the device were mapped using the standards purchased from Merck, Germany. A control sample was also included. A reference standard with a known concentration of elements was used to ensure the quality and establish the accuracy of the heavy metal estimation results of ICP spectrometry. Ten, 10 samples were selected from each species for analysis and the validation of analysis. The recovery of each element was within an acceptable range (80-120%) as shown in Table 1. All arsenic and elemental concentrations are reported in mg/kg on a dry weight basis. We used the mean values for the concentration of each element because the replication of the none of the single values of the three samples was statistically significant at a CI of 95%; thus, the mean value was used. All these analyzes were done in the central laboratory of Ferdowsi University of Mashhad.

Table 1. Detection limit and recovery rate of inductively coupled plasma spectrometer for different trace elements

Element	Result obtained	Certified value	*CV (%)	Recovery value (%)	LOD	LOQ
As	0.62	0.54	5.6×10^{-4}	87.09	0.027	0.08
Cr	0.76	0.82	2.3×10^{-5}	107.89	0.049	0.11
Cu	6.3	6.1	4.6×10^{-4}	96.82	0.082	0.21
Co	0.74	0.71	4.2×10^{-5}	95.94	0.066	0.14
Cd	0.023	0.019	3.3×10^{-5}	82.60	0.0008	0.0013
Hg	0.25	0.23	3.4×10^{-5}	92	0.00072	0.002
Pb	1.5	1.32	4.04×10^{-5}	88	0.0013	0.025
Ni	34.5	35.6	3.41×10^{-5}	103.18	0.093	0.22
Zn	56	57.9	5.84×10^{-5}	103.39	0.056	0.17
Mn	0.23	0.26	3.16×10^{-5}	113.04	0.043	0.091
Fe	78	82	6.6×10^{-5}	105.11	0.26	0.65

*CV: Coefficient of variation;** LOD: Limit of Detection;***LOQ: Limit of quantification

Health risk assessment

The present study mainly aimed to measure the health risk of exposure to heavy metals by consuming the fish sold in the city of Mashhad. The calculations were done for two populations of adults and children. To this aim, the risk assessment model developed by the US Environmental Protection Agency was used. The risk assessment is defined as attempts to identify and quantify the risk caused by a specific chemical substance to human health. In doing so, the potential adverse effects of the chemical are considered if consumed at the recommended amount or more if exposed in any possible way [16].

Chronic daily intake (CDI) of heavy metals

To estimate the daily intake of heavy metals through consuming edible fish tissue in the two groups (adults and children), the following formula was used.

$$CDI= (C\times IR\times EF\times ED)/ BW\times AT$$ (1. Estimated (average daily intake through consuming fish)

To estimate the maximum permissible intake for the two age groups, firstly, the amount of daily intake had to be compared to the standard permissible limit set by the WHO and the Food and Agriculture Organization of the United Nations. If the daily intake exceeded the standard limit, the amount of edible fish tissue needed to be reduced to reach the permissible limit [5, 6].

Target hazard quotient (THQ)

Estimating the target hazard quotient serves to represent the non-carcinogenic effects of consuming a certain stuff on the population. It is the ratio of the daily intake of heavy metals to the standard amount. If the estimated value is lower than 1, it indicates the absence of any carcinogenic effect. If the value is higher than 1, it shows the possibility of carcinogenic effects [17]. In this study, the standard values were those suggested by the American Environmental Protection Agency (Table 2-3). This parameter fails to estimate the hazard of diseases other than cancer. It only shows the relationship between hazard and exposure to pollutants. Since exposure to two or more pollutants may increase the effects or interactive effects, in this research, the value of the cumulative non-carcinogenic risk was estimated by summing up the risk of consuming the metals and reported as the total non-carcinogenic risk [17, 18].

$$THQ= CDI/RFD$$

$$HI = \sum THQ1 + THQ2 +THQ3 + ...$$ (2: Estimated non-carcinogenic risk)

Cancer risk (CR)

The cancer risk indicates the probability of a person developing cancer in lifetime due to exposure to a potential carcinogen. As for carcinogenic substances, it is assumed that there is a linear positive correlation between exposure to the pollutant concentration and the risk of cancer. The resulting slope in this relationship is the *cancer slope factor* measured as the milligrams of chemical substance taken in per kilogram of body weight per day [17, 18]. The probability of a person developing any type of cancer throughout life is considered to be caused by exposure to various types of pollutants. Equation 3 is used to estimate the cancer risk. The values for the variables in the equation are provided in Tables 2.

$$CR = EDI \times OSF \quad \text{(3. Estimated cancer risk)}$$

Statistical procedure and sample size

SPSS was used to analyze the results. To check the normality of distribution, Kalmogorov-Smirnov test was used. To compare the concentration of pollutants in fish samples, one-way ANOVA was run for normal data, and Kruskal-Wallis test for non-normal data. To describe data, descriptive statistics (frequency, mean, standard deviation) were used as well as a test of analysis of variance (comparison between changes of the variables).

Table 2. Health risk assessment variables of commercial fish in Iran Market.

Variables	Value	Unit
Tolerable Daily Intake (EDI)	Tables 3 and 4	mg kg^{-1} bw day^{-1}
Oral Reference Dose (RFD)	As=0.0003, Cd=0.001, Al=0.7, Co=0.0004, Cu=0.04, Fe=0.7, Hg=0.0004, Zn=0.3, Cr=0.003, Ni=0.02, Pb=0.0035, Ba= 0.07	mg kg^{-1} day^{-1}
Oral Slope Factor (OSF)	As=1.5, Pb=0.0085, Cd=0.38	mg kg^{-1} day^{-1}
Concentration (C)	Table 2	mg kg^{-1}
Body Weight (BW)	Adult: 70, Child: 20	kg
Exposure frequency (EF)	365	Days per years
Exposure duration (ED)	Adult: 70, Child: 6	Years
Ingestion Rate (IR)	Adult: 29, Child: 19	g kg^{-1} day^{-1}
Averaging time (AT)	Adult: 10550, Child: 2100	Days
Target Hazard Quotient (THQ)	Table 5; Safe: 10> HQ ; Possible non-cancer risk and need action: 10< HI	
Hazard Index (HI)	Table 5	
Cancer Risk (CR)	Table 6 ; Safe: 10^{-6} >CR; Moderate Risk or Borderline; $10^{-6} < CR < 10^{-4}$; High Risk: $10^{-4} < CR$	

RESULTS

Concentration of heavy metals in the edible tissue of fish

In this research, the concentration of 11 heavy metals was estimated which were found in the edible tissue of 9 fish species sold in Mashhad. Table 3 shows the concentration of heavy metals and the mean value for each metal in the edible tissue of the commonly used fish in Mashhad. The results showed that among the 11 metals, the concentration of chromium, cobalt, lead, zinc, and manganese was higher than the standards set by the World Health Organization and food and agriculture in the edible tissues of fish coming from the South Sea. The concentration of lead and zinc in the samples from the Caspian Sea basin and the fish farms was higher than the standard limit. Also, variation in the concentration of cobalt, mercury, zinc and manganese among different fish samples of the Caspian Sea, the South Sea and farmed fish showed a significant difference ($p < 0.05$). However, the variation in other heavy metals (arsenic, chromium, copper, cadmium, lead and nickel) was not significantly different among different species ($p > 0.05$).

Table 3. Concentration of heavy metals and the average amount of each metal in the edible tissue of fish

Elements		Persian Gulf and Oman sea (n=50)				Caspian Sea (n=20)		Cultivate fish (n=20)				
mg kg^{-1}	***Standard**	***S. commerson***	**O.ruber**	**P. argenteus**	**L. johnii**	**R. kutum**	**M.Cephalu**	***S. morpha fario***	**H. molitrix**	**Average**	**SD**	**[a]p-value**
As	1	0.57± 0.12	0.45±0.28	0.48± 0.09	0.64± 0.12	0.34±0.07	0.68±0.12	0.39±0.13	0.56±0.12	0.513	0.119	0.065
Cr	1	1.23± 0.28	1.11±0.65	1.5±0.21	1.09± 0.023	0.8±0.12	0.94±0.07	0.59±0.76	0.86±0.21	1.015	0.280	0.059
Cu	30	23.7± 4.57	20.58±12.6	23.41±4.8	16.8± 3.9	23.27±3.8	28.61±4.6	19.5±0.54	28.77±6.8	23.08	4.174	0.087
Co	0.04-0.26	0.85± 0.12	0.63±0.15	0.56±0.092	0.93±0.15	0.11±0.023	0.25±0.03	0.14±0.05	0.21±0.09	0.46	0.325	0.023
Cd		0.061±0.02	0.076±0.02	0.032±0.012	0.05± 0.021	0.024±0.01	0.058±0.2	0.023±0.012	0.05±0.01	0.047	0.019	0.072
Hg	0.5	0.23± 0.04	0.46±0.13	0.14±0.035	0.34±0.11	0.18±0.023	0.32±0.11	0.12±0.076	0.39±0.11	0.272	0.123	0.043
Pb	0.5	0.73±0.29	0.61±0.19	0.78±0.26	0.89± 0.065	0.52±0.14	0.58±0.16	0.44±0.12	0.71±0.23	0.657	0.147	0.17
Ni	80	50.77±0.23	38.7±2.8	42.48±11.5	69.7±10.3	50.34±7.7	60.68±10.4	50.13±8.7	70.4±16.8	54.06	11.613	0.27
Zn	30	50.23±18.8	50.11±11.45	31.94±5.8	72±9.3	19.8±2.9	27.14±7.5	25.9±5.7	33.17±9.8	38.78	17.332	0.034
Mn	1	2.83±0.82	2.71±0.56	2.54±1.25	1.04±0.023	0.45±0.11	0.79±0.25	0.24±0.11	0.61±0.27	1.40	1.09	0.021
Fe	100	59.77±29.5	67.9±16.8	52.48±9.4	87±10.46	42.34±12.6	76.68±9.8	82.67±11.6	92.9±23.6	70.22	17.73	0.082

SD and ± Standard deviation; [a]: the statistically significant difference in the concentration of heavy metals between different species; *nd:* Values below the limit of detection (LOD); *n*: number of samples; Scomberomorus commerso, Otolithes ruber, Pampus argenteus, Lutjanus johnii, Rutilus kutum; Mugil Cephalus, S. t. morpha fario, Hipophthalmichthys molitrix; *Standard based on WHO/FAO

Daily intake of heavy metals

The daily intake of heavy metals through consuming fish was estimated and the findings are summarized in Table 4 and Figure 1. The estimated intake is presented per unit of body weight (μg kg^{-1} body weight per day). As the results for the two age groups (adults and children) showed, the mean daily intake of heavy metals followed a specific order: iron > nickel > zinc > copper > manganese > chromium > lead > arsenic > cobalt > mercury > cadmium. Iron, nickel and zinc had the highest level of intake, while mercury and cadmium had the lowest level of metal intake.

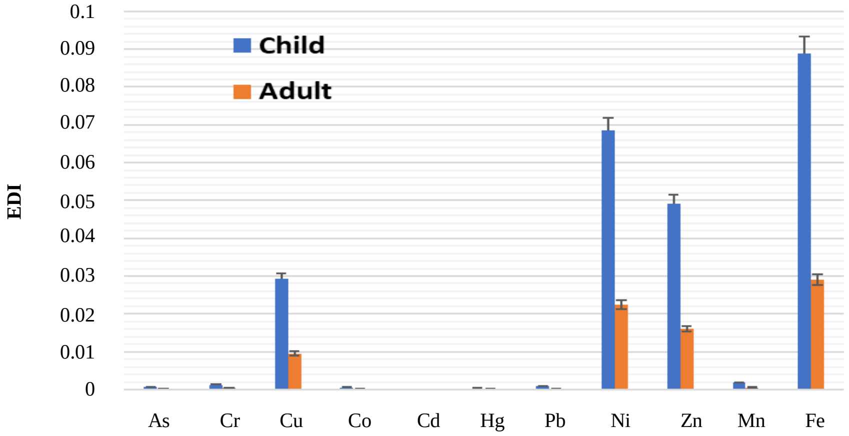

Figure 1. Contribution of arsenic and heavy metals on daily intake in different heavy metals.

Table 4. Estimated dietary intake (EDI) of heavy metals and arsenic by consuming edible tissue of fish in adult and child population

Adult population (mg kg^{-1} bw day^{-1})									Average	SD
Elements	***S. commerson***	**O. ruber**	**P. argenteus**	**L. johnii**	**R. kutum**	**M. Cephalus**	***S. t. morpha fario***	**H. molitrix**		
As	0.00020	0.00018	0.00019	0.0002	0.00014	0.0002	0.00016	0.0002	0.00021	4.94E-05
Cr	0.00051	0.00046	0.00062	0.00045	0.00033	0.00038	0.00024	0.00035	0.00042	0.00011
Cu	0.0098	0.0085	0.0096	0.0069	0.009	0.011	0.008	0.011	0.0095	0.0017
Co	0.00035	0.0002	0.0002	0.0003	4.56E-05	0.00010	0.000058	0.000087	0.00019	0.00013
Cd	2.53E-05	3.15E-05	1.33E-05	2.32E-05	9.94E-06	2.4E-05	9.53E-06	2.07E-05	1.96E-05	7.947E-06
Hg	9.53E-05	0.00019	0.00005	0.00014	7.46E-05	0.00013	4.97E-05	0.00016	0.00011	5.120E-05
Pb	0.0003	0.00025	0.00032	0.00036	0.00021	0.00024	0.00018	0.00029	0.00027	6.095E-05
Ni	0.021	0.016	0.0175	0.028	0.020	0.025	0.020	0.029	0.022	0.0048
Zn	0.020	0.020	0.013	0.029	0.008	0.011	0.010	0.013	0.0160	0.0071
Mn	0.0011	0.0011	0.001	0.0004	0.00018	0.0003	9.94E-05	0.00025	0.00058	0.00045
Fe	0.024	0.028	0.021	0.036	0.017	0.031	0.034	0.038	0.029	0.0073
Child population										
As	0.0007	0.00057	0.0006	0.0008	0.00043	0.0008	0.00049	0.0007	0.00065	0.00015
Cr	0.0015	0.0014	0.0019	0.0013	0.0010	0.0011	0.00074	0.001	0.0012	0.00035
Cu	0.030	0.026	0.029	0.021	0.029	0.036	0.02	0.036	0.029	0.005
Co	0.0010	0.00079	0.00070	0.0011	0.00013	0.00031	0.00017	0.00026	0.00058	0.0004
Cd	7.73E-05	9.63E-05	4.05E-05	7.09E-05	3.04E-05	7.35E-05	2.91E-05	6.33E-05	6.02E-05	2.43E-05
Hg	0.00029	0.00058	0.00017	0.00043	0.00022	0.00040	0.00015	0.00049	0.00034	0.00015
Pb	0.00092	0.00077	0.00098	0.0011	0.00065	0.00073	0.00055	0.00089	0.00083	0.00018
Ni	0.064	0.049	0.053	0.08	0.063	0.076	0.063	0.089	0.068	0.014
Zn	0.063	0.063	0.040	0.091	0.025	0.034	0.032	0.042	0.049	0.021
Mn	0.0035	0.003	0.0032	0.0013	0.0005	0.001	0.0003	0.0007	0.001	0.0013
Fe	0.075	0.086	0.066	0.11	0.053	0.097	0.10	0.11	0.088	0.022

SD standard deviation; Estimated Daily Intake (EDI)

Non-carcinogenic risk

The present study estimated non-carcinogenic hazard quotient (HQ), hazard index (HI) and carcinogenic risk (CR) of heavy metals caused by the consumption of edible fish tissue in adults and children. As the results of analyzing 11 metals in 8 species of fish showed, the risk index for adults in all species of fish was lower than the borderline of 1, but the hazard quotient for all of them was higher than 1, with a mean value of 0.33 ± 2.09 ranging between 1.3 and 2.86. As the statistical findings showed, the hazard index was significantly different across metals, and as it can be seen, the non-carcinogenic hazard quotient of chromium and cobalt varied significantly among different species. Also, among the 11 metals investigated, the hazard index for children was higher than the borderline of 1 in only two metals, lead and zinc. However, similar to adults, the hazard quotient for all of them was higher than 1, with a mean value of 6.39±1.60 which ranged between 4.21 and 8.77. As the statistical findings showed, the hazard index was significantly different across metals. The non-carcinogenic hazard quotient of chromium, cobalt, lead, zinc and manganese had the highest level among all species. Also, the tabulated findings show that the hazard index for children was 2.5 to 3 times as high as adults (Table 5 and Figure 2).

Table 5. Non-cancer of arsenic and heavy metals from fish consumption in child and adults.

Elements	THQ: Adult population									
	S. commer-son	O. ruber	P. argenteus	L. johnii	R. kutum	M. Cepha-lus	*S. t. morpha fario*	H. molitrix	THQ m± SD	*P-values
As	0.079	0.062	0.066	0.088	0.047	0.094	0.054	0.077	0.07±0.01	0.074
Cr	0.170	0.153	0.207	0.151	0.110	0.130	0.081	0.119	0.14±0.03	0.001
Cu	0.245	0.213	0.242	0.174	0.241	0.296	0.202	0.298	0.23±0.04	0.062
Co	0.176	0.131	0.116	0.193	0.023	0.052	0.029	0.044	0.11±0.07	0.001
Cd	0.025	0.031	0.013	0.023	0.010	0.024	0.010	0.021	0.02±0.008	0.072
Hg	0.024	0.048	0.015	0.035	0.019	0.033	0.012	0.040	0.028±0.12	0.081
Pb	0.756	0.632	0.808	0.922	0.539	0.601	0.456	0.735	0.68±0.15	0.035
Ni	0.105	0.080	0.088	0.143	0.104	0.126	0.104	0.146	0.11±0.043	0.13
Zn	0.694	0.692	0.441	0.994	0.273	0.375	0.358	0.458	0.53±0.23	0.032
Mn	0.255	0.244	0.229	0.094	0.041	0.071	0.022	0.055	0.12±0.09	0.001
Fe	0.035	0.040	0.031	0.051	0.025	0.045	0.049	0.055	0.04±0.01	0.058
HI	2.564	2.326	2.256	2.868	1.432	1.847	1.376	2.048	2.09±0.33	0.001
****P-values**	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	
THQ: Child Population										
As	0.24	0.19	0.20	0.27	0.14	0.29	0.16	0.24	0.22±0.05	**0.11**
Cr	0.52	0.47	0.63	0.46	0.34	0.40	0.25	0.36	0.43±0.12	0.037
Cu	0.75	0.65	0.74	0.53	0.74	0.91	0.62	0.91	0.73±0.13	0.086
Co	0.54	0.40	0.35	0.59	0.07	0.16	0.09	0.13	0.29±0.21	0.001
Cd	0.08	0.10	0.04	0.07	0.03	0.07	0.03	0.06	0.06±0.02	0.24
Hg	0.07	0.15	0.04	0.11	0.06	0.10	0.04	0.12	0.09±0.04	0.123
Pb	2.31	1.93	2.47	2.82	1.65	1.84	1.39	2.25	2.08±0.47	0.001
Ni	0.32	0.25	0.27	0.44	0.32	0.38	0.32	0.45	0.34±0.07	0.058
Zn	2.12	2.12	1.35	3.04	0.84	1.15	1.09	1.40	1.64±0.73	0.001
Mn	0.78	0.75	0.70	0.29	0.12	0.22	0.07	0.17	0.39±0.30	0.001
Fe	0.11	0.12	0.09	0.16	0.08	0.14	0.15	0.17	0.13±0.03	0.28
HI	7.84	7.11	6.90	8.77	4.38	5.65	4.21	6.26	6.39±1.60	0.001
****P-values**	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	

Red color shows High risk (unsafe level) of THQ (target hazard quotient) and HI (hazard index); m± SD and ± is mean and standard deviation; *the statistically significant difference in the level of THQ between different species; **the statistically significant difference in level of THQ between different elements.

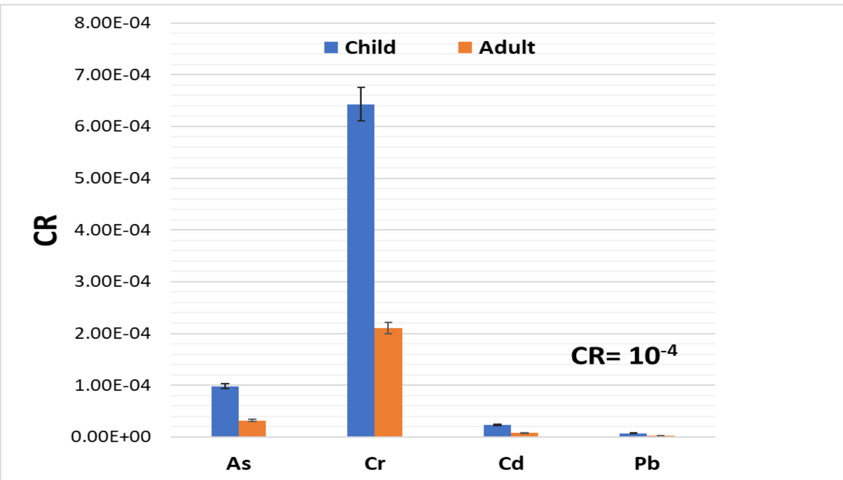

Figure 2. Carcinogenesis risk index of heavy metals through the consumption of edible tissue of fish in all the examined samples.

Carcinogenic risk

The present study estimated the carcinogenic risk (CR) of 4 metals, including arsenic, chromium, cadmium and lead, through consuming edible fish tissue in two age groups of adults and children. Among adults, three metals including arsenic, cadmium and lead were within the safe range (CR≥1×10^{-4}) and only chromium was in the borderline of carcinogenic risk, varying between 1.22×10^{-4} and 3.11×10^{-4}. As the statistical findings showed, the carcinogenesis risk of arsenic and chromium was significantly different. In the studies conducted on children population, cadmium and lead are in the safe range (CR≥1×10^{-4}) and arsenic and chromium are in the borderline of carcinogenic risk, and the variations are respectively 6.46×10^{-5}, 1.29×10^{-4}, 3.74×10^{-4} and 9.50×10^{-4} (Table 6).

Table 6. Cancer risk of arsenic and heavy metals from fish consumption in child and adults.

Elements	*S. commerson*	O. ruber	P. argenteus	L. johnii	R. kutum	M. Cephalus	*S. t. morpha fario*	H. molitrix	Average	*p-value
CR: Adult population										
As	3.54E-05	2.80E-05	2.98E-05	3.98E-05	2.11E-05	4.23E-05	2.42E-05	3.48E-05	3.19E-05±7.41E-06	0.001
Cr	2.55E-04	2.30E-04	3.11E-04	2.26E-04	1.66E-04	1.95E-04	1.22E-04	1.78E-04	2.10E-04± 5.82E-05	0.001
Cd	9.60314E-06	1.2E-05	5.04E-06	8.82E-06	3.78E-06	9.13E-06	3.62E-06	7.87E-06	7.48E-06±3.02E-06	0.075
Pb	2.57064E-06	2.15E-06	2.75E-06	3.13E-06	1.83E-06	2.04E-06	1.55E-06	2.5E-06	2.32E-06±5.18E-07	0.12
TCR	3.02E-04	2.72E-04	3.48E-04	2.78E-04	1.92E-04	2.48E-04	1.52E-04	2.23E-04	2.52E-04±6.25E-05	0.032
****p-value**	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	
CR: Child population										
As	1.08E-04	8.55E-05	9.12E-05	1.22E-04	6.46E-05	1.29E-04	7.41E-05	1.06E-04	9.76E-05±2.27E-05	0.026
Cr	7.79E-04	7.03E-04	9.50E-04	6.90E-04	5.07E-04	5.95E-04	3.74E-04	5.45E-04	6.43E-04±1.78E-04	0.016
Cd	2.93E-05	3.66E-05	1.54E-05	2.7E-05	1.16E-05	2.79E-05	1.11E-05	2.41E-05	2.29E-05±9.23E-06	0.16
Pb	7.85E-06	6.57E-06	8.4E-06	9.58E-06	5.6E-06	6.24E-06	4.74E-06	7.64E-06	7.08E-06±1.58E-06	0.21
TCR	9.25E-04	8.32E-04	1.07E-03	8.48E-04	5.88E-04	7.59E-04	4.64E-04	6.83E-04	7.70E-04±1.91E-04	0.018
****P-value**	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	

±: Standard deviation; Carcinogenic Risk (CR); *the statistically significant difference in the level of cancer risk between different species; **the statistically significant difference in the level of cancer risk between different elements.

DISCUSSION

With the spread of environmental pollutants and the possibility of entrance in the food chain, it is important to explore the types of pollution and food hygiene. Contamination of food with heavy metals is a major health issue due to the high toxicity, stability of structure, limited degradability and high accumulation capability of some heavy metals in human body and the adverse effects on society [2].

Normally, aquatic muscles are among the major tissues used to measure the concentration of heavy metals, as they are edible and can dramatically affect human health. Heavy metals enter human body in different ways, but eating contaminated fish is a common way to intake heavy metals. Thus, the present study investigated fish muscle tissues in human nutrition [19, 20]. Due to the toxicity of heavy metals, regulatory bodies worldwide have set permissible limits on these pollutants in certain food stuff such as fish. Several studies showed that the mean concentration of essential and non-essential metals in fish varies greatly. Accumulation of heavy metals in tissues and its relationship with growth factors in fish are affected by several factors. Instances are the length, weight, species, aquatic physiological condition, metabolism and regulatory activities of body homeostasis, growth process, concentration and retention time of metals in water, metabolic activity, exposure time and environmental factors (salinity, pH and temperature). Any specific function of metals in tissues depends on a network of the biochemical factors of the tissue and biological factors, the effect of increasing the growth of tissue (dilution property of the concentration of metals) and metabolic rate of species, half-life of metals and their availability in the habitat [21].

The concentration of metals in the fish tissues was compared with the maximum permissible limit suggested for human consumption according to international standards (Tables 1-4). The estimated mean concentration of all 11 metals in the target species was compared with the standards set by the WHO. The results showed the concentration of copper, nickel, cadmium, mercury, iron, and arsenic in all species was less than the maximum permissible limit (Tables 1-4).

There seems to be no threat of contamination. However, the concentration of chromium, cobalt, lead, zinc, and manganese in the species transported from the South Sea was higher than the maximum limit. Considering the potential risks of toxicity of the above metals, consuming these species of fish by children and pregnant women should be only with caution. Studies show that different factors can affect the accumulation of heavy metals in fish muscle tissues, such as the different management of each region, environmental conditions, sewage discharge, existence of industrial factories and aquaculture activities in different regions [22-27]. The possible ways of introducing heavy metals into water in the South Sea are the economic activity of Mahshahr port, oil and gas extraction and relevant mechanisms, shipping, cultivation of agricultural products. Also, Bandar Imam Petrochemical and Arvand Petrochemical are located in Mahshahr Special Economic Zone. These have turned the coasts of the southern province into one of the most polluted areas in the country [28].

The results of some research by Nasralehzadeh et al. (2012) on the accumulated heavy metals in the edible tissue of carp showed the amounts of nickel, cadmium and lead metals in the muscle of the Caspian sea carp was not high and remained below the permissible limit set by the European Union, the WHO, the Australian Health Association, the UK Department of Agriculture, Fisheries and Food, the Food and Drug Administration and several other countries (New Zealand, Hong Kong, Denmark and Switzerland). In the muscle tissues of carp, accumulated mercury complied with the standards set by the WHO and was lower than the standard limit set by the Food and Drug Administration (FDA) [23]. Bandani et al. (2008) investigated the concentration of heavy metals (lead, cadmium, chromium, zinc) in the muscle tissue and liver of carp fish in the coast of Golestan province. This study showed that zinc had the highest concentration in fish muscle tissue. Next ranked lead, cadmium and chromium. Comparison of the concentration of heavy metals in this study with international standards showed their concentration in muscle tissues and liver of carp fish was less than the permissible limit [24]. The results showed that the amount of lead and mercury in silver pomfret was lower than the WHO international standard [29]. Turkman et al. (2005) contended that the concentration of heavy metals in fish muscles can be greatly varied depending on the place of fishing and the species of fish[1]. These researchers also showed that concentration of heavy metals in different species of fish varied significantly in sampling from different regions [26]. In another study, Fabrice et al. (2006) found that concentration of heavy metals such as arsenic, cadmium and mercury in abalone, lobster and groundfish depended on the place where the fish lived. They also found significant differences between the concentration of elements in species in different areas of Victoria coast in Australia. However, there was no consistent pattern or trend in the concentration of heavy metals in these areas [27].

The statistical findings of a body of related research show that the accumulation of some heavy metals such as cobalt, mercury, zinc and manganese in the edible tissue of different fish species is significantly different from each other.

Usually, the concentration of metals varies depending on the species of fish, which is due to the different degrees of movement and activity, food amounts and other behaviors. Nutritional habits and carnivorous diets of, as well as the positioning of these species at the end of the food chain, are other factors that can increase the accumulation of some heavy metals [30, 31]. The physiological condition of fish can affect the bioaccumulation of any metal. The accumulation level of different metals in tissues also depends on their physiological role, though muscles do not rank first in the biological transfer and accumulation of metals. In polluted water habitats, the concentration of metals in fish muscles may exceed the permissible limit for human consumption, so they can turn into a major threat to human health. The heavy metals lead, cadmium, mercury, arsenic and chromium belong to the category of unnecessary and toxic metals. They lack any known function in biochemical processes. These metals have a high potential for bioconcentration and accumulation in different organs of fish [32]. Due to the increased load of pollutants entering water, more attention is paid to risk management and food security assessment of the ingredients of household food basket.

Although seafood is among major consumer goods, it is far from logical to consume it regardless of food security issues. One point to note in consuming fish is to consider the adequate amount so that the level of the desired metal in body does not exceed the standard limit [33]. Despite the benefits of consuming fish, today, due to the presence of pollutants in aquatic ecosystems, there are different risks especially for more susceptible populations such as children and pregnant women. Fish consumption should be assessed through scientific methods. However, consuming fish is only one way of exposure to heavy metals, and by consuming other foods such as rice, wheat and vegetables, the effects on the consumers may intensify.

Although eating is a major way of taking in pollution, unlike air or water, this way of taking pollutants in is not the same across communities or cities (due to different personal tastes). Thus, its intake rate is a function of the way of eating [34]. Since the food culture in Iran is varying in scope and food habits, it is neither possible nor valid to come up with a single pattern for the standard intake rate in food products. For this reason, in most countries of the world, there are different estimations of the standard concentration of pollutants in food, which is mostly influenced by eating habits, specific climatic features, industry and agriculture. This index has necessarily led to different regional standards, which can even diverge from the standards set by the WHO. As for marine and aquatic products, this difference is greater because the rate of consumption varies in different provinces, and for this reason, it is not possible to consider a single pattern of use for the whole population. Therefore, the standard limit should be set according to criteria such as per capita consumption, toxicity, consumer characteristics (women, men, and children) and potential intake [35-40].

As the findings showed, the estimated hazard quotient of the metals arsenic, iron, zinc, chromium, copper, cobalt, nickel, cadmium, mercury and lead (all 11 metals) for adults consumed orally was lower than is 1. Therefore, there is no possibility of non-carcinogenic effects of these metals after consuming fish. However, among children, the hazard quotient was higher than 1 for the two metals, lead and zinc. As already discussed in the results, despite the presence of large amounts of lead, zinc, copper, chromium, cobalt, nickel and manganese metals in fish samples, the hazard index for both age groups was higher than 1, and this index was higher in children than in adults. This problem can be due to the higher ratio of fish consumption per capita to the average weight in the children population, compared to the adult population [41]. Considering that the hazard index was higher than 1, there was a significant health risk for consumers [16, 17, 42 and 43].

In 2014, Hasanpour et al. investigated the nutritional risk of lead, cadmium, zinc and copper metals in white fish in the southern coast of Mazandaran Sea. The results showed no threat of consuming white fish in terms of the toxic metals [44]. Idris et al. (2015) measured the concentration of zinc, copper, lead and cadmium in 13 fish species in the Joro River in Malaysia. The hazard quotient of zinc (0.19-0.76), cadmium (0.18-0.40), lead (0.40-1.25) and copper (0.08-0.36) was reported in this study. These results showed that the hazard quotient of zinc and copper in all species was less than 1, but in the case of cadmium and lead, these values were higher than 1 in 6 and 5 species, respectively (92). Alipour et al. (2013) measured the concentration of lead and cadmium in the muscle of Kalame fish in the Miankala lagoon. Their results showed that the hazard quotient of lead (9.88×10^{-5}) and cadmium (9.88×10^{-5}) were lower than 1. Among these metals, lead had the highest hazard quotient (93). In 2013, Pahanande et al. estimated the concentration of lead, chromium and cadmium in two species of duck fish and common carp in Anzali lagoon. Compared to international standards, the amount of lead in these two species was 0.51 and 0.31 mg/kg, respectively, higher than the standard set by the WHO. However, the content of the two elements cadmium and chromium in the muscle tissue showed values lower than the standard. Besides, the highest amount of daily consumption was that of lead, as found in the duck fish species of Anzali lagoon [45]. In another study, Tawil et al. (2013) measured the concentration of copper, zinc, lead, nickel and cadmium in tilapia fish. Their results showed that the hazard quotient for metals was lower than 1, which is consistent with the results of the present study [46]. Mortazavi Saravi et al. (2013) reported that the hazard of cadmium, lead, zinc, copper and mercury in carp in the southern coast of the Caspian Sea was lower than the maximum permissible limit [47].

Fish is considered a major food all over the world, especially for those living near the sea. Nutritionists recommend that people include fish in their food chain to enjoy the health benefits. Yet there are chances of accumulating metals in fish body tissues. Thus, caution should be taken in consuming fish [23, 24]. The potential hazards of metals show that people should not only consume small amounts of contaminated food, but also consider variety in food consumption to avoid lifetime intake of heavy metals. The knowledge of contaminants is not widely available to the general public on commonly used fish, indicating a need for more information on contaminant levels in fish in specific areas [48]. Information on the precise identification of contaminants in species of fish, where the contaminants accumulate most, and the permissible limits of consuming contaminants in the fish in a certain region of the world can help people make informed decisions on consuming the lowest quantity of metals [19]. Mortazavi et al. (2013) estimated the risk of taking in some metals through consuming silver and salted pomfret in Hormozgan province. The results showed that the estimated hazard quotient was significantly lower than 1. Thus, there was no hazard to the consumption of these fish species, which is consistent with the present study [49]. Selagi estimated the non-carcinogenic risk of consuming cadmium and zinc in carp in Zarivar lagoon, and found no potential adverse effects on health [50].

The length of time (in years) human can be exposed to a source of pollution is estimated at 70 years by the US Environmental Protection Agency. It can represent the average life expectancy of the general population [51]. As for the carcinogenic effects, all exposures to risk factors during one's life accumulate together, and finally, at almost any time in life, they can emerge as a type of cancer. Meanwhile, non-carcinogenic effects appear only during exposure. Therefore, the time taken for the emergence of carcinogenic effects differs from the average time taken for the emergence of non-carcinogenic effects [52, 53].

The present study compared the estimated carcinogenic risk with the maximum permissible value suggested by the US Environmental Protection Agency, which is 1×10^{-6} to 1×10^{-4}. It shows a high risk for the health of children and adults. In other words, the incidence of cancer caused by chromium and arsenic elements in children and chromium in adults through consuming fish in Mashhad has been estimated at more than one in ten thousand in children and adults. Sharfi et al. (2017) assessed the carcinogenic risk of the heavy metals lead and cadmium caused by consuming 9 species of fish in Bandar Abbas. They found the carcinogenic risk of both metals was less than the permissible limit of developing cancer in lifetime (60). NarottamSaha et al., in a seasonal survey of heavy metals in Bay of Bengal fish and the assessment of carcinogenic risk, showed that consumers were at the risk of carcinogenicity caused by arsenic metal. For other metals, especially lead and cadmium, there was no carcinogenic risk (CR $<10^{-5}$) [54].

Limitations and strengths

There are certain limitations to the risk assessment that can adversely affect the validity of findings. These are summarized here: 1)fish consumption and body weight were estimated based on the EPA standard, 2) risk assessment as the Cancer Slope Factor (CSF) was calculated only for arsenic, lead, chromium, and cadmium, as there are currently no actual CSFs for the other heavy metals, 3) CSF was assumed to be constant for all individuals, but in fact CSF can vary across individuals, 4) the risk assessment model was used only based on the concentration of heavy metals, but in fact, fish can contain other chemical pollutants. As explained above and due to the risk variation in values higher than 1×10^{-4} in all samples, the estimated risk level in the fish consumed in Mashhad can be higher than the estimated values in this study.

CONCLUSIONS

Sea food is the main food source, it is rich in essential nutrients which have an important effect on human health; it affect positively energy and nutrient intakes. The results showed that in comparison to national and international standards, the concentration of heavy metals, chromium, cobalt, lead, zinc and manganese were higher, so it is likely that the presence of heavy metals in fish samples consumed in Mashhad city adversely affect people's health. Moreover, the non-carcinogenic risk assessment showed that the fish species consumed in Mashhad are exposed to heavy metal contamination more than the permissible limit. The hazard index of lead and zinc elements in fish samples was more than 1 among children, which is considered hazardous. The carcinogenic risk assessment indicated a high risk to people's health. The incidence of cancer caused by these elements through fish consumption in all areas of Mashhad was estimated to be more than one in ten thousand children and adults. In risk assessment, there are possible limitations that need to be considered and may partly affect the estimated values. Therefore, the real level of risk in fish consumed in Mashhad may be higher than the estimated values in this study. Also, since in the current study, the carcinogenic risk in all samples was estimated at10^{-4}, there is a possibility that the risk will increase with the passage of time due to the increasing number of pollutants.

Therefore, it is recommended to continuously monitor fish in terms of the contained heavy metals or residual chemical toxins to maintain food security, because the results of these monitoring can be used as a basis for decision-making in improving people's health. Due to the dearth of research on persistent toxic pollutants in protein supplies of human nutrition, it is of a great importance to monitor and evaluate aquatic food sources and determine the carcinogenic risk of these sources to human health. There are hopes that the present findings help improve the country's health standards and inform decision-making to improve human health.

ACKNOWLEDGEMENTS

The authors wish to express their gratitude towards the vice president of research in Mashhad University of Medical Sciences, the chiefs and staffs of the health centers and the esteemed participants. This research was funded by the Mashhad University of Medical Sciences (project number: 971698).

ETHICAL CONSIDERATION

Ethics approval and consent to participate. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1398.182) after obtaining the required permit for the research.

Conflict of interests

The authors declare that they have no conflict of interests.

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