



Metal Risk Assessment Study of Canned Fish Available on the Iranian Market

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Received: 17 July 2020 / Accepted: 18 October 2020 / Published online: 10 November 2020
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Abstract

Iran is the largest fishery producer in the region reaching nearly 1 million tons. Fish provide a good many nutrients that are beneficial for our health. Due to significant deposits of xenobiotics in the water environments, however, fish may also be a source of non-essential metals, causing a variety of disorders. The main challenges to Iranian fisheries are environmental pollution and quality control, so this study aims to estimate the concentration of cadmium (Cd), mercury (Hg), nickel (Ni), and lead (Pb) in canned tuna fish produced and consumed in Iran. We studied four popular brands ($N = 4 \times 20$) with ICP-MS and then looked at the concentrations and calculated the risk assessment parameters. We found that the lowest concentration was observed for Cd (18 $\mu\text{g}/\text{kg}$) and the highest for Ni (132 $\mu\text{g}/\text{kg}$). Among the brands studied, Pb concentrations differed most (42.0 to 113.3 $\mu\text{g}/\text{kg}$) and Hg levels were more consistent (24.0 and 39.4 $\mu\text{g}/\text{kg}$). The concentrations of Cd, Hg, and Pb in all the brands tested were below EU permissible thresholds. The intake estimation risk assessment parameters (EDI, contribution to PTWI, and CR) and non-cancer risk assessment parameters based on reference doses (THQ and HI) demonstrated the safety of tested products in respect to all metal concentrations studied, while the parameters regarding the toxic effects (MoE, and ILCR) showed that the consumption might cause health risks in terms of Cd (ILCR), Ni (ILCR), and Pb (MoE). The consumption of the canned fish studied should therefore be maintained at a reasonable level (2–5 meals containing fish weekly), so that it may provide necessary nutrients, while avoiding the health risk due to metal content.

Keywords Food safety · THQ · MoE · Cancer risk · Non-cancer risk

Highlights

- Metal concentrations varied significantly between brands studied.
- All concentrations were lower than permissible levels.
- Pb concentrations were high enough to cause non-cancer risk.
- Cancer risk caused by Cd and Ni levels are borderline safe.
- Due to metal levels, consumption should be kept at a reasonable level.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12011-020-02446-8>.

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Introduction

Canned tuna fish is a popular type of seafood available on the market worldwide. In Iran the significant increase in the number of factories producing canned fish from 134 in 2007 to 569 in 2013 illustrates the high rate of supply and consumption, which increased from 9.0 kg per capita in 1961 to 20.3 kg in 2015 [1, 2]. In many countries fish provide up to 20% of the animal protein consumed, so fishing and fish farming contribute significantly to the food security [3]. Fish and fish products are a valuable source of proteins, micronutrients, fat-soluble vitamins, and polyunsaturated fatty acids, including omega-3 acids, which protect the cardiovascular system and ensure the right proportions of fatty acids in biological membranes [4, 5]. As well as benefits, however, the consumption of fish may also pose a risk to consumers [6, 7]. Industrialization and agriculture have caused metal pollution of aquatic environments [8, 9]. Fish and marine predators are at the top of the aquatic food chain, so they are greatly influenced by bioaccumulation and biomagnification [10]. Seafood is therefore considered a significant source of human exposure to metals [11–13]. Such exposure may be a serious danger to human health [10]. One of the most important fish food parameters to be monitored is therefore the concentration of metals.

Metals such as cadmium, lead, and mercury are dangerous environmental pollutants, so their permissible levels in food have been established by the European Union: 100 µg/kg, 300 µg/kg, and 1000 µg/kg respectively for Tuna fish; 50 µg/kg, 300 µg/kg, and 500 µg/kg respectively for Caspian kutum [14]. In the case of lead, the ALARA approach (As Low As Reasonably Achievable) has recently been recommended [4, 15]. Despite potential toxicity, permissible levels of other metals, such as nickel, have not been regulated, probably due to their lower general influence and environmental levels. In some circumstances, however, where their concentrations are increased, they too may be harmful. In the case of nickel, its genotoxic and carcinogenic properties in vertebrates are generally known [16, 17]. An important source of nickel in processed food, such as canned fish, as well as environmental pollution, is packaging and stainless-steel equipment used in processing [18]. As well as permissible thresholds, risk assessment parameters could also be used in order to evaluate the consequence of consumer exposure to metals [19]. Surprisingly, despite the popularity of canned fish in Iran, almost no risk assessment data is available in the literature. This is a significant gap in the knowledge and may result in poor decisions in policy and the unnecessary exposure of consumers [20]. We therefore planned our research to study metal concentrations and their danger to consumers in fish available on the Iranian market to fulfill the aforementioned lack of knowledge.

Hence, the main aim of the study was to measure cadmium (Cd), mercury (Hg), nickel (Ni), and lead (Pb) concentrations in four brands of canned fish produced in Iran. Based on the concentrations found, the risk assessment parameters (estimated daily intake, contribution to provisional tolerable weekly intake, maximum allowable fish consumption rate, target hazard quotient, hazard index, margin of exposure, and incremental lifetime cancer risk) were calculated to address the question on consumption safety. The relationships between the elements were also studied.

Materials and Methods

Cans of the four most popular brands of tuna fish (20 units per brand) were bought from groceries, markets, supermarkets, hypermarkets, and major food distribution networks in Sanandaj city (Iran) between March and July 2018. They included one of or a mixture of the two species of yellowfin tuna (*Thunnus albacares*), longtail tuna (*Thunnus tonggol*), and Caspian kutum (*Rutilus kutum*). In order to protect manufacturers' details, brands were randomly coded as A, B, C, and D, where brand A contained yellowfin tuna, brands B and C contained yellowfin tuna and longtail tuna, and brand D contained yellowfin tuna and Caspian kutum. Information about the proportion of the species in two species cans were not presented on the cans. Thus, for our calculations, we assumed the proportions of the species in brands B, C, and D were equal.

Metal Analyses

All the brands included the same type of oil which was drained off after opening each can oil. Then, the meat was homogenized thoroughly in a food blender (Persia France Digital Blender PR-444, France); 1 g was weighed (accuracy to 0.0001 g; GR200 balance, A&D, Japan) and transferred to a mineralization vessel. Prior to measuring metal concentrations, samples were mineralized via the open mineralization system. The sample was then supplemented with 10 ml of nitric acid (suprapure HNO₃, 65%, Merck, Germany), left for one night to slowly digest, and finally supplemented with 5 ml of perchloric acid (ultrapure HClO₄, 70%, Merck, Germany). The samples were then placed in a water bath (TW12, Julabo, Germany) in 100 °C until reaching a clear solution point. The solutions were then transferred into 25-ml flasks, topped up with ultrapure water (Fistream, WSC044 model, UK), and passed through a filter (0.45-µm filter) into the plastic tubes of a spectrometer.

All metal concentrations were measured with an ICP-MS spectrometer (Agilent 7900, Agilent Technologies, USA). All the standard solutions were prepared according to the Merck standards of a concentration of 1000 mg/L. The limits of

detection for each metal in the final samples were as follows: Cd 1.5, Hg 1.0, Pb 2.5, and Ni 1.5 $\mu\text{g}/\text{kg}$. Spikes were used to monitor quality and they yielded mean recoveries of 104%, 96%, 106%, and 93% respectively. The operation parameters for ICP-MS were as follows: radiofrequency power 1.5 kW; plasma gas flow rate 15 L/min; carrier gas flow 1.01 L/min; make up gas 0.15 L/min; sample uptake rate 1.7; sample depth: 10 mm, auto detector mode, peak hopping 3 sweep per reading, 3 readings per replicate. The concentrations measured in solutions were recalculated to $\mu\text{g}/\text{g}$ of wet weight. In order to check the accuracy and precision of measurements, blank samples in each batch of digestion (whose concentrations were further subtracted from the concentrations in the test samples) and certified reference material (DORM-2 Dogfish Muscle) were used (Table 1).

Risk Assessment Parameters

We included three groups of risk assessment parameters in the protocol: intake estimation, and non-cancer and cancer risk parameter groups. The first group (intake estimation risk assessment parameters) included estimated daily intake (EDI), contribution to provisional tolerable weekly intake (PTWI), and maximum allowable consumption rate (CR_{lim} and CR_{mm}). The second group (non-cancer risk assessment parameters) included target hazard quotient (THQ), hazard index (HI), and margin of exposure (MoE). The third group (cancer risk assessment parameters) included incremental lifetime cancer risk (ILCR). The equations used for the calculation of the abovementioned parameters as well as their general meaning are presented in the [Appendix \[21–25\]](#).

Statistical Analysis

Prior to the analysis, data distribution and homogeneity were evaluated to check whether they met the assumptions of parametric protocols. Since the evaluation gave positive results, data were described with means and standard deviations (SD). One-way ANOVA followed by a Tukey post hoc test was performed to assess the differences in metal concentrations between brands. The relationships between metal levels in

particular brands were estimated with Pearson's correlation coefficients. The significance level was set at 0.05. The analysis was performed using Statistica 13 software (Statsoft, Tibco Software, USA).

Results

Concentrations of Metals

Mean concentrations of metals varied significantly between brands of the canned fish studied (Table 2). There was no unanimous scheme of ascending concentrations across all the brands, but (with the exception of Brand A) Hg most often demonstrated the lowest mean concentrations ranging from 24.0 $\mu\text{g}/\text{kg}$ (brand B) to 39.4 $\mu\text{g}/\text{kg}$ (brand D) with the lowest variation, too. The highest mean concentrations in all the brands were noted for Ni reaching 132.6 $\mu\text{g}/\text{kg}$ (brand A). Concentrations of Cd and Pb were intermediate between Hg and Ni and revealed the highest variation between brands. Their highest concentrations reached 71.2 $\mu\text{g}/\text{kg}$ (Cd in brand D) and 113.3 $\mu\text{g}/\text{kg}$ (Pb in brand B) (Fig. 1, Table 2).

No strong correlations (Pearson $r > 0.6$) between metal concentrations in canned fish studied were observed.

Risk Assessment Parameters

EDI values ranged from 9.77E-06 for Cd to 7.2E-05 mg/kg bw/day for Ni (both noted in brand A). The biggest differences between brands were noted for Pb, and the lowest for Hg (Table 3). Contribution to PTWI (not available for Ni) fell between 0.64% for Pb and 3.86% for Cd, both in brand D. CR_{lim} varied widely between the metals, the lowest mean observed for Pb in brand B (0.06 kg/day) and the highest for Ni in brand C (18.27 kg/day). The number of allowable meals per month (CR_{mm}) consequently ranged between 8.28 and 2450.06 (Table 3).

In THQ values, the order $\text{Ni} < \text{Cd} < \text{Hg} < \text{Pb}$ was observed in all four brands. The most similar values were found for Hg and the largest variation was recorded for Pb (Table 4). HI, which summed them up, was the lowest in brand D (0.45) and the highest in brand B (0.76). MoE values varied significantly between metals with the lowest values obtained for Pb ranging from 10.24 to 27.61 for nephrotoxicity and from 24.38 to 65.74 for cardiovascular effects. The highest values were observed for Ni reaching 1023.1 in brand A (Table 4).

ILCR (unavailable for Hg) values noted for Pb were the lowest and ranged from 1.94E-07 in brand D to 5.23E-07 in brand B. ILCR values noted for Cd and Ni were higher, ranging from 1.47E-05 (brand A) to 5.80E-05 (brand D) and from 3.79E-05 (brand C) to 6.55E-05 (brand A) (Table 5).

Table 1 Comparisons of certified and measured concentrations ($\mu\text{g}/\text{g}$) of metals studied in the certified reference material (DORM-2 Dogfish Muscle; $N = 7$)

Metal	Certificated	Measured	Recovery (%)
Cd	0.043 \pm 0.004	0.045 \pm 0.005	104.6
Hg	4.64 \pm 0.24	4.46 \pm 0.18	96.1
Ni	19.4 \pm 2.8	18.60 \pm 1.75	95.9
Pb	0.065 \pm 0.006	0.068 \pm 0.009	104.6

Table 2 Mean levels of metals (µg/kg) with SD in different brands of canned fish (20 units per brand) followed by a statistical comparison between brands (one-way ANOVA with Tukey post hoc test)

Metal	Brand A	Brand B	Brand C	Brand D	F	p
Cd	18.0 (7.9) ^a	30.8 (16.7) ^a	60.8 (22.8) ^b	71.2 (26.7) ^b	31.33	< 0.001
Hg	32.1 (8.5) ^{c, d}	24.0 (5.7) ^a	39.4 (6.5) ^b	33.9 (7.7) ^{b, d}	15.57	< 0.001
Ni	132.6 (21.1) ^a	122.6 (16.9) ^{a, c}	76.6 (18.7) ^b	111.9 (21.4) ^c	30.67	< 0.001
Pb	59.3 (16.7) ^b	113.3 (33.9) ^a	62.0 (13.8) ^b	42.0 (39.7) ^b	25.47	< 0.001

Different letters indicate statistically significant differences between brands(tested for each metal separately)

Discussion

We found that among the brands studied Hg levels differed the least, while Pb levels differed the most. Statistically significant differences in metal concentrations were found, but no general pattern of concentrations was observed in the brands tested. A significant variation was therefore also observed in the risk assessment parameters. Strong correlations between metal concentrations were not observed.

Concentrations of Metals

Cd concentrations in all brands tested were more than three times higher than in another Iranian study of canned tuna fish [29]. Similarly, Canadian, Indian, and Italian studies revealed lower Cd concentrations than in brands B, C, and D [30, 31]. Hg levels on the other hand were found to be considerably lower than Cd levels observed in canned tuna fish from India (650 µg/kg), Canada (600 µg/kg), USA (180 µg/kg), and Iran (110 µg/kg) [29, 30, 32]. Results obtained for Pb (with the exception of brand B) were comparable to another Iranian study on canned tuna fish, but higher than noted in Italy (10 µg/kg) and Morocco (20.1 µg/kg) [30, 31, 33]. In the literature, the lowest Ni concentrations in fish (82 µg/kg) were noted in blue whiting (*Micromesistius poutassou*) and saurel (*Trachurus symmetricus*) and the highest level (58,980 µg/kg) was found in Indian tire-track eel (*Mastacembelus armatus*)

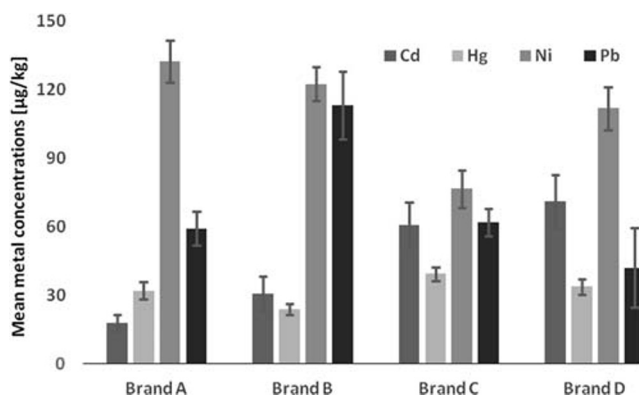


Fig. 1 Mean levels of metals (bars) with 95% confidence intervals (whiskers) in canned fish studied

[10, 34]. We found Ni concentrations close to the lower above-mentioned values and even lower than those observed in canned tuna fish marketed in Egypt (370 µg/kg) and other parts of Iran (580–1040 µg/kg) [35, 36].

The accumulation of metals in fish depends on various environmental conditions as well as on the biology of particular species [37]. The levels of metals in canned fish may result from handling and processing [38]. Observed disparities in concentrations between the brands studied may be also related to different species, the age, and the size of fish used in the manufacturing process [39–41]. They may, in turn, arise from different fishing grounds, where contrasting water properties may be a consequence of a variety of agricultural, domestic, and industrial activities [42, 43]. The fishing date may

Table 3 Risk assessment parameters* linked to intake estimation based on metal levels in canned fish studied

Metal	Parameter	Brand A	Brand B	Brand C	Brand D
Cd	EDI	9.77E-06	1.67E-05	3.30E-05	3.86E-05
	PTWI%	0.98	1.67	3.3	3.86
	CR _{lim}	3.89	2.27	1.15	0.98
	CR _{mm}	521.34	304.27	154.49	131.88
Hg	EDI	1.74E-05	1.30E-05	2.14E-05	1.84E-05
	PTWI%	3.05	2.28	3.74	3.22
	CR _{lim}	0.22	0.29	0.18	0.21
	CR _{mm}	29.23	39.17	23.85	27.68
Ni	EDI	7.20E-05	6.65E-05	4.16E-05	6.07E-05
	PTWI%**	-	-	-	-
	CR _{lim}	10.56	11.42	18.27	12.52
	CR _{mm}	1416.18	1531.6	2450.06	1678.23
Pb	EDI	3.22E-05	6.15E-05	3.36E-05	2.28E-05
	PTWI%	0.9	1.72	0.94	0.64
	CR _{lim}	0.12	0.06	0.11	0.17
	CR _{mm}	15.81	8.28	15.15	22.33

*EDI, estimated daily intake [mg/kg body weight per day]; PTWI%, contribution to provisional tolerable weekly intake; CR_{lim}, maximum allowable consumption rate [kg per day]; CR_{mm}, maximum allowable consumption rate [meals per month]

**No PTWI value has been established for Ni

Table 4 Non-cancer risk parameters* based on metal levels in different brands of canned fish studied

Metal	Parameter	Brand A	Brand B	Brand C	Brand D
Cd	THQ	0.0098	0.0167	0.033	0.0386
	MoE	1023.1	597.1	303.2	258.8
Hg	THQ	0.174	0.130	0.214	0.184
	MoE	516	692	421	489
Ni	THQ	0.0036	0.0033	0.0021	0.0030
	MoE	69,500	75,100	120,000	82,300
Pb	THQ	0.322	0.615	0.336	0.228
	MoE	19.55 ^a ; 46.55 ^b	10.24 ^a ; 24.38 ^b	18.73 ^a ; 44.60 ^b	27.61 ^a ; 65.74 ^b
All	HI	0.51	0.76	0.58	0.45

*MoE (margin of exposure) values were calculated for the following endpoints: Cd—renal cortex dysfunction; Hg—subjective and objective evidence of autonomic dysfunctions; Ni—decreased body and organ weights; Pb—(a) nephrotoxicity, (b) cardiovascular effects [15, 26–28]

be a source of such differences as well, because accumulation rate changes with the season with its peak during summer [44]. We have not found strong relationships between metals accumulated in fish. If such a correlation had been noted, we would have suspected that the source of metals was mutual e.g., polluted water and sediments [45, 46]. Another source of metals, specific for this type of product, can be oil included in cans. However, oil is not suspected of having effects on fish products because it represents minor levels of metals [47].

The permissible levels for metals in tuna fish in Europe and Iran were set as 100 µg/kg for Cd, 1000 µg/kg for Hg, and 300 µg/kg for Pb. For Caspian kutum, these levels are 50 µg/kg, 500 µg/kg, and 300 µg/kg respectively [48]. In all the brands tested, Cd, Hg, and Pb concentrations were below the permissible thresholds. Cd concentrations ranged from 18.0% (brand D) to 94.9% (brand B) of its permissible limit. Pb concentrations reached up to 37.8% (brand A) of its limit and Hg levels up to 4.5% (brand B). European and Iranian regulations provide no permissible level of Ni in fish.

Risk Assessment Parameters

EDI values expressed as % of RfD were from lowest to highest for Ni (from 0.21 to 0.36% RfD), for Cd (from 0.98 to 3.86% RfD), for Hg (from 13.01 to 21.37% RfD), and for Pb (from 22.82 to 61.53% RfD), which indicates

Table 5 Incremental lifetime cancer risk values based on metal levels in different brands of canned fish

Metal	Brand A	Brand B	Brand C	Brand D
Cd	1.47E-05	2.51E-05	4.95E-05	5.80E-05
Ni	6.55E-05	6.06E-05	3.79E-05	5.53E-05
Pb	2.74E-07	5.23E-07	2.86E-07	1.94E-07

that Pb contamination may serve as a limiting factor in the consumption of the products tested [49]. The contribution to PTWI for all metals tested was low, with the highest values noted for Cd (from 0.98 to 3.86%) followed by Hg (from 2.28 to 3.74%), suggesting that mean fish consumption in Iran causes rather low exposure to the metals tested (Table 6). It should be noted that the PTWI thresholds were already withdrawn for Cd and Pb due to long-life of these elements in the human body, their high toxicity, and cases of adverse effects caused by concentrations on PTWI levels [50]. In the case of Cd, provisional tolerable monthly intake (PTMI) is considered now as an appropriate reference value, which was established on the level of 25 µg/kg bw [50]. In our study, the contribution to PTMI was safe for all brands with an average value of 3.01% (range between 1.21 and 4.75%). According to ALARA approach, no substitute value has been proposed for Pb PTWI, still suggesting limiting the exposure as much as possible [4, 15, 50].

Due to benefits of eating fish, the WHO recommends eating fish meals 1 or 2 times a week [51]. US EPA and FDA recommend that fish species with low Hg levels should be consumed 2 or 3 times a week, and with medium Hg levels (such as tuna fish) once a week [52]. According to CR parameters for Hg, depending on the brand, consumers may eat between 4.7 and 7.6 times more of the fish tested per day than the average daily fish consumption (38 g) in Iran. The canned fish studied may safely (in terms of Hg) be eaten 6 to 10 times a week. Bearing in mind Pb, daily fish consumption could be 1.6 to 4.5 times higher than the current daily fish consumption in Iran with weekly permissible number of meals between 2 and 6. CR values for Pb and Hg indicated that these metals put a limit on the safe level of consumption of the products tested. CR parameters noted for Cd and Ni allow for much higher fish consumption. Compared to other studies, CR parameters

Table 6 Summary of evaluation of fitness for human consumption, based on risk assessment parameters

Metal	Parameter	Brand A	Brand B	Brand C	Brand D	
Cd	Conc. threshold	Safe	Safe	Safe	Safe	
	EDI	Safe	Safe	Safe	Safe	
	PTWI%	Safe	Safe	Safe	Safe	
	PTMI%	Safe	Safe	Safe	Safe	
	CR _{mm}	Safe	Safe	Safe	Safe	
	THQ	Safe	Safe	Safe	Safe	
	MoE*	Safe	Safe	Safe	Safe	
	ILCR	Threshold	Threshold	Threshold	Threshold	
Hg	Conc. threshold	Safe	Safe	Safe	Safe	
	EDI	Safe	Safe	Safe	Safe	
	PTWI%	Safe	Safe	Safe	Safe	
	CR _{mm}	Safe	Safe	Safe	Safe	
	THQ	Safe	Safe	Safe	Safe	
	MoE*	Safe	Safe	Safe	Safe	
	ILCR**	-	-	-	-	
	Conc. threshold**	-	-	-	-	
Ni	EDI	Safe	Safe	Safe	Safe	
	PTWI%**	-	-	-	-	
	CR _{mm}	Safe	Safe	Safe	Safe	
	THQ	Safe	Safe	Safe	Safe	
	MoE*	Safe	Safe	Safe	Safe	
	ILCR	Threshold	Threshold	Threshold	Threshold	
	Pb	Conc. threshold	Safe	Safe	Safe	Safe
		EDI	Safe	Safe	Safe	Safe
PTWI%		Safe	Safe	Safe	Safe	
CR _{mm}		Safe	Safe	Safe	Safe	
THQ		Safe	Safe	Safe	Safe	
MoE*		Unsafe	Unsafe	Unsafe	Unsafe	
ILCR		Safe	Safe	Safe	Safe	

*Pb MoE for both endpoints

**Parameters not calculated due to lack of official regulations

reported for silver carp indicated safer Pb concentrations, but at the same time more dangerous concentrations of Cd and Ni [12].

Data in the literature show various levels of THQ, which occasionally exceed the safety threshold, e.g., in Tire-track eel from India [10], and most often allow safe consumption of the fish under examination here [9, 12, 53]. Summing up the THQs obtained in our study HI confirmed that the exposure through consumption would cause no adverse non-cancer effects in consumers: all values were below 1 for all brands [54]. Similar conclusions were reached based on MoE for Cd, Hg, and Ni. In the case of Pb, however, MoE suggested an increased risk for consumers in the context of nephrotoxicity and cardiovascular effects for all the brands studied: MoE values below 100 [55]. Both THQ

and MoE indicated a non-cancer risk posed by consumption, but they have a different sensitivity. That discrepancy comes from the fact that MoE refers to NOAEL (not observed adverse effects level), and THQ to RfD of a given metal. NOAEL represents the highest dose, at which toxic or adverse effects are not observed [56], whereas RfD represents daily exposure dose that is unlikely to cause adverse effects.

The probability of lifetime health cancer risk (ILCR) values calculated for Cd and Ni in our study was below $10E-4$ (a threshold established for increased probability), but still higher than $10E-06$, when the concentration of tested contaminant should not cause cancer [56]. Obtained ILCR values for Cd and Ni are therefore on the threshold, whereas for Pb are at a safe level.

Conclusion

In all the brands of canned fish studied, metal concentrations were below the permissible thresholds established for fish meat. Due to the large variation in particular metal concentrations between brands, however, it is difficult to identify the safest brand. Intake estimation parameters (EDI, contribution to PTWI, CR_{lim}, and CR_{mm}), as well as some non-cancer risk assessment parameters (THQ and HI), confirmed safe levels, while MoE for Pb indicated consumption that may pose a cardiovascular risk or nephrotoxicity. ILCR, on the other hand, revealed that concentrations of Cd and Ni are on the cusp of safety in respect of cancer risk.

We conclude that the consumption of the canned fish studied should be kept at a reasonable level (according to the most restricting Pb risk parameters: between 2 and 5 meals weekly, depending on the brand, which is still higher than the recommendation of WHO and US EPA) so that it may provide the necessary nutrients, while avoiding posing a health risk.

Acknowledgments We sincerely thank the Environmental Health Research Center for its contribution.

Funding Kurdistan University of Medical Sciences supported this research (grant number: 1397.032; Ethical code: IR.MUK.REC.1397.032).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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