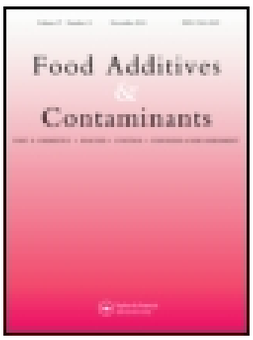

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Exposure to metals and arsenic from yellow and red tuna consumption

Luca Maria Chiesa[a], Federica Ceriani[a], Antonio Procopio [b], Sonia Bonacci[b], Renato Malandra[c], Sara Panseri[a] and Francesco Arioli[a]

[a]Department of Health, Animal Science and Food Safety, University of Milan, Milan, Italy; [b]Dipartimento di Scienze della Salute, Università Magna Græcia, Catanzaro, Italy; [c]Director of Veterinary Unit, ATS Milano-Città Metropolitana, Milan, Italy

ABSTRACT

Tuna is one of the most frequently consumed fish and, as a predator, can biomagnify pollutants. Metal and other elements pollution is an important worldwide concern. Based on these considerations, the aim of this work was to investigate the occurrence of As, Cd, Cr, Ni, Hg and Pb in tuna coming from different FAO areas to evaluate human exposure. The analysis was performed on muscle tissues through a quadrupole inductively coupled mass spectrometry. One hundred thirty-one samples were analysed. One red tuna from the Adriatic Sea and 11 yellow tunas exceeded Pb maximum levels (MLs) with a concentration ranging 0.31–0.86 mg kg^{-1}; three red tunas from different Mediterranean sub-areas exceeded Hg MLs, with a concentration range 1.19 to 1.80 mg kg^{-1}. All the Hazard Indexes (HIs) were lower than one, indicating that only a negligible health hazard could derive from the ingestion of tuna, for both average and high consumers. The risk of carcinogenicity from Cr is still under debate at the concentrations detectable in food.

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Tuna; arsenic; metals; risk; hazard index

Introduction

Fish is an excellent source of high-value protein rich in essential amino acids and micro and macro elements, and has an advantageous fatty acid profile, resulting from the content of essential polyunsaturated fatty acids, known to support good health (Usydus et al. 2009). Tuna is one of the most frequently consumed and commercially attractive fish worldwide (Ikem and Egiebor 2005).

Tuna, as a predator, is a high-performance fish with very high metabolism rates; thus, having high food intake rates, it increases the accumulation of pollutants (Voegborlo et al. 1999). Pollution by metal and other elements in fish is an important word wide concern due to the health risk associated with fish consumption and diet is the main route of exposure. Many metals naturally occurring in the environment, including copper, iron, manganese, nickel, and zinc have important biological roles. However, a significant number of metals, like cadmium, lead, and mercury have no biological roles, but have highly toxic properties when consumed by animals, including humans, and are classified as toxic metals (Chen et al. 2016). The World Health Organization lists cadmium, lead, and mercury in its list of top ten chemicals of major public health concern (WHO 2016) and exposure to these metals has been linked to numerous neurodevelopmental and neurodegenerative disorders in humans (Von Stackelberg et al. 2015). Inorganic arsenic (As) has been linked to increased risk of cancer of the skin, lungs and bladder, and skin lesions. Other symptoms associated with chronic arsenic exposure are peripheral neuropathy, encephalopathy, hepatomegaly, bone marrow depression, diabetes and renal function impairment (EFSA 2009a). Inorganic arsenic was the first element to be identified as a human carcinogen and the IARC allocated it to Group 1(IARC 2012a). Cadmium (Cd) can damage kidneys and cause poor reproductive capacity, hypertension, and hepatic dysfunction (Abou-Arab et al. 1996). The kidney is the critical target organ for dietary exposure to cadmium and renal damage is characterised by cadmium accumulation in convoluted proximal tubules (EFSA 2009b). Data on exposure to Cd have also been associated with an

CONTACT Sara Panseri sara.panseri@unimi.it Department of Health, Animal Science and Food Safety, University of Milan, Via Celoria 10, Milan 20133, Italy

increased risk of lung cancer through inhalation by workers or smokers, and bladder, endometrium, testicular, pancreatic and gall bladder cancer (Huff et al. 2007; EFSA 2009b). No sure causal association between Cd oral exposition and cancer is currently available (European Commission (EC) 2007) even if some recent data seem to indicate an association with cancer at low dietary exposures (Åkesson et al. 2014). However, studies on dietary exposure to Cd did not show an increase of incidence of total or specific cancers in 90,000 Japanese of both sexes (Sawada et al. 2012), and of breast cancer in 30,000 U.S. postmenopausal women (Adams et al. 2012). Consequently, even if IARC (IARC 2012b) allocates Cd in Group 1, information regarding the carcinogenetic effect of Cd is still incomplete for risk assessment by oral intake. Mercury (Hg) has been associated with neurotoxicity, ototoxicity, tremors, irritability, memory problems, changes in vision and hearing. Moreover, it has been associated with developmental toxicity and cardiovascular disease (EFSA 2012). The critical target for acute toxicity of mercury is the kidney followed by the liver, nervous system, immune system, reproductive and developmental systems. Nickel (Ni) is classified by IARC (IARC 2012a) as a human carcinogen causing cancers of the lung, nasal cavity and paranasal sinuses only after inhalation and studies on animals did not give any evidence of oral carcinogenicity. Oral absorption of Ni can elicit eczematous flare-up reactions in the skin in Ni-sensitised individuals (EFSA 2015). Some other metals (e.g. chromium) cause nephropathy, anuria, neurotoxicity and embryotoxicity (EFSA 2014b). Lead (Pb) causes nervous dysfunction, kidney damage and chronic toxicity, poor reproductive capacity, hypertension, tumours, hepatic dysfunction and may cause miscarriage in pregnant women (EFSA 2010). The risk from exposure to As and metals requires further comment. The European Commission (European Commission (EC) No 1881/2006 2006) set maximum levels (MLs) for Cd (0.10 mg kg^{-1}), Pb (0.30 mg kg^{-1}) and for Hg (0.1 mg kg^{-1}) in tuna. No MLs have yet been established by the European Union for As, Cr and Ni (EU). EFSA established a $BMDL_{01}$ for As between 0.3 and 8 μg/kg b.w. day^{-1} for an increased risk of cancer to lung, skin and bladder, and skin lesions (EFSA 2009a). Cd is a primary toxic on the kidney and may cause renal dysfunction (EFSA 2009b). The CONTAM panel defined a tolerable weekly intake (TWI) of 2.5 μg kg^{-1} b.w. In 2014, EFSA suggested a tolerable daily intake (TDI) for Cr (III) of 300 μg kg^{-1} body weight, which was based on reproduction and developmental toxicity reported in some studies and from a long-term study on rats of the US National Toxicology Programme (NTP) (NTP 2010). Cr (VI), classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1), is not present in food, considered a strong reducing medium (EFSA 2014b). Hg TWI (1.3 μg g^{-1}) expressed as total Hg is derived from neurodevelopmental toxicity (EFSA 2012). The TDI for Ni is 2.8 μg kg^{-1} body weight, a value derived from studies about the incidence of litters with post-implantation loss in rats. Considered the possibility of eczematous and allergic reactions elicited by acute oral exposure a $BMDL_{10}$ of 1.1 μg Ni kg^{-1} body weight, with a margin of exposure (MOE) of 10 or higher, accounting for the variability of the immune response in nickel-sensitised individuals is also stated (EFSA 2015). The critical effects of Pb are developmental neurotoxicity in infants and children ($BMDL_{01}$ = 0.50 μg kg^{-1} day^{-1}), cardiovascular effects and prevalence of chronic kidney disease (CKD) in adults ($BMDL_{01}$ = 1.50 μg kg^{-1} day^{-1} and $BMDL_{10}$ = 0.63 μg kg^{-1} day^{-1}, respectively) (EFSA 2010). Infants (aged 0–3 years) are more exposed than children (5–10 years) and adults since Pb is better absorbed in growth plates than bone tissues. The International Agency for Research on Cancer classified inorganic lead as probably carcinogenic to humans (Group 2A) in 2006, for limited evidence of carcinogenicity in humans and sufficient evidence in animals (NTP 2004; IARC 2006). However, since the doses used to induce tumours in rats are very high compared to human intake, EFSA considered human exposure to lead through food unlikely to represent a significant cancer risk (EFSA 2010).

Several studies are present in the literature on the presence of metals in fish (Table 1). The aim of this work is to investigate the occurrence of As, Cd, Cr, Ni, Hg, Pb in tuna coming from different Fishing Areas (FAO) to evaluate human intake.

Table 1. Concentration of As and metals in tuna from literature analysed by ICP-MS.

Reference	Element	Area	Concentration range (μg g^{-1}w.w.)
Voegborlo et al. 1999	Hg	Libya	0.20–0.66
	Cd		0.09–0.32
	Pb		0.18–0.40
Storelli and Marcotrigiano 2001	Hg	Mediterranean Area	0.07–4.26
Storelli et al. 2005	As	Mediterranean	1.62–5.01
	Cd	Area	0.01–0.04
	Hg		0.13–0.35
	Pb		0.07–0.18
Licata et al. 2005	Cd	Sicily	n.d.-0.26
	Hg		2.45–4.21
	Pb		n.d.-0.24
Storelli et al. 2010	Cd	Mediterranean	n.d.-0.03
	Hg	Area	0.07–1.76
	Pb		n.d.-0.33
Guérin et al. 2001	Cr	France	0.22[a]
	Ni		0.34[a]
	Pb		0.011[a]
Mol 2011	Cd	Turkey	0.01–0.02
	Hg		0.06–0.30
	Pb		0.09–0.45
Olmedo et al. 2013	As	Spain	0.033[b]
	Cd		0.008[b]
	Hg		0.00[b]
	Pb		0.004[b]

Materials and methods

Chemicals and reagents

Nitric acid (HNO_3, ≥69.0%, Trace SELECT) and hydrogen peroxide (H_2O_2 ≥ 30% Trace SELECT Ultra) were purchased from Fluka analytical (Germany). Hydrochloric acid Superpure was purchased from Carlo Erba. Purified water was obtained through a Milli-Q Integral 5 system (Millipore, Merck KGaA, Darmstadt, Germany).

Standards

Two multielement standards solution: IV-ICPMS -71A containing 10 μg ml^{-1} of arsenic (As), aluminium (Al), cadmium (Cd), chromium (Cr), manganese (Mg), nickel (Ni), lead (Pb), zinc (Zn), and CMS-1 containing 10 μg ml^{-1} of yttrium (Y), were purchased from Inorganic Ventures (Christiansburg, Virginia, USA). Mercury standard solution containing 1000 mg L^{-1} was purchased from Fluka. IV-ICPMS-71A and mercury standard solutions were used daily to prepare calibration standards in 2% HNO_3/HCl (1:1). Standard 100 μg L^{-1} yttrium solution was prepared daily and added to all samples as internal standard, to verify changes in instrumental sensitivity.

Sample collection

A total of 131 of red tuna (*Thunnus thynnus)* and yellow tuna (*Thunnus albacares*) samples were collected from March 2017 until October 2017, at the wholesale Milan fish market, which supplies the whole country. Their origin was chosen randomly with the aim of simulating the tuna consumption of an Italian consumer. The FAO areas are shown in Table 2. The edible part was finely dispersed with an Ultraturrax (IKA®-Werke GmbH and Co. KG, Staufen, Germany) at 13500 rpm for 2 min. All samples were stored at −20°C, until analysis.

Sample preparation

The sample preparation was carried out using an Anton Paar Multiwave 3000 digestion system equipped with a XF100 rotor. To decontaminate PTFE vessels, a cleaning procedure was carried out by adding 4 ml of HNO_3 and 4 ml of H_2O in each vessel, in the following conditions: 1100 W for 15 min. After cleaning, vessels were rinsed with ultrapure water and dried. Aliquots of 0.5 g of each homogenised sample were weighted directly into the PTFE vessel of the microwave system. The digestion was performed by adding 1 ml of H_2O, 4 ml of HNO_3, 0.5 ml of HCl and 0.5 ml of H_2O_2. The operating conditions used for the microwave digestion were 800 W over 15 min and held at this power for 30 min. After digestion, samples were quantitatively transferred to a graduated polypropylene test tube and diluted with ultrapure water to 50 ml. The analytical batch consisted of a set of calibration standard, samples, and a minimum of three procedural blanks. A midrange calibration standard was analysed after each batch of 15 samples to verify instrumental drift throughout the

Table 2. Tuna sample details: number of samples, species, FAO area, country of origin.

Species	FAO Area	Country	Total
Red Tuna *(Thunnus thynnus)*	27	Spain VIIIC-	3
		North Spain	2
	37	Sicily-Adriatic Sea	8
			4
Yellow Tuna *(Thunnus albacares)*	51	Maldive-	15
		Indian Ocean	
	57	Maldive-Sri Lanka-Indian Ocean	47
	71	Pacific Ocean	52
Total			**131**

run. Seven-point calibration curves covering the range 0.01–100 μg L^{-1} were used for quantitative analysis. Standard solutions were prepared by diluting the multielement solutions.

ICP-MS analyses

The analysis was performed by a quadrupole inductively coupled mass spectrometry, X Series 2 (Thermo Scientific, Waltham, MA, USA), equipped with a collision cell incorporating kinetic energy discrimination which efficiently eliminates matrix, argon and based spectral interferences using reaction gases He/H_2 (97:3). The sample solutions were pumped by a peristaltic pump from tubes arranged on CETAC ASX-520 auto-sampler (Thermo Scientific, Omaha, NE, USA). Argon and He/H2 (9:7) mixture were used pure, at 99.999%. Instrument sensitivity, resolution and mass calibration were optimised daily with the tuning solution (Multielement Tune A, containing 10 μg L^{-1} of Ba, Be, Bi, Ce, Co, In, Li, Ni, Pb, U in 2% HNO_3, to maximise ion signals and to minimise interferences effects due to high oxide levels ($CeO^+/Ce^+ < 2\%$) and doubly charged ions ($Ba^{2+}/Ba^+ < 3\%$). In order to verify the robustness of the analytical method, Yttrium was added as internal standard and analysed with the run. Sample data were qualified following the Internal Standard Recovery method, and required to be within a 80–120% limit.

Statistical analysis

Statistical analysis was performed using GraphPad InStat version 3.00, GraphPad Software, San Diego California USA. The comparison between FAO areas was made through the Kruskal–Wallis Test (Nonparametric ANOVA) for samples with non-Gaussian distribution and Dunn's Multiple Comparisons Test when a significant difference was found. *P* was set at 0.05.

Results and discussion

Table 3 shows the data relative to metal concentration in tuna tissues and the differences between the various sampling areas. The Mediterranean Sea samples show the maximum concentrations for As (5.53 mg kg^{-1}), Cd (0.034 mg kg^{-1}), Cr (0.216 mg kg^{-1}), Hg (1.80 mg kg^{-1}) and Ni (0.319 mg kg^{-1}). Based on the results reported in Table 3 the estimated daily intakes (EDI) with tuna of an average European consumer, for any considered element, were calculated as: EDI = [(highest value between mean and median concentration in tuna) x annual tuna intake]/(365 days x 60 kg body

Table 3. Mean ± SD, minimum, median and maximum concentration of each metal and comparison from different FAO zones. Concentrations expressed as mg kg^{-1} muscle.

		FAO 27 *N* = 5	FAO 37 *N* = 12	FAO 51 *N* = 15	FAO 57 *N* = 47	FAO 71 N = 52	TOTAL N = 133
As	Mean±SD	0.93 ± 0.30	2.29 ± 1.63	1.06 ± 0.48	1.28 ± 0.53	1.02 ± 0.39	1.23 ± 0.73
	Minimum	0.55	0.34	0.37	0.44	0.56	0.34
	Median	0.85	2.41	0.90	1.15	1.00	1.06
	Maximum	1.33	5.52	2.01	3.11	1.72	5.52
Cd	Mean±SD	0.017 ± 0.003	0.018 ± 0.007	0.017 ± 0.005	0.013 ± 0.005	0.014 ± 0.004	0.014 ± 0.005
	Minimum	0.015	0.008	0.008	0.007	0.006	0.006
	Median	0.016	0.017	0.017	0.011	0.014	0.014
	Maximum	0.023	0.034	0.026	0.025	0.028	0.034
Cr	Mean±SD	0.039 ± 0.027	0.037 ± 0.024	0.050 ± 0.045	0.042 ± 0.033 (a)	0.053 ± 0.029	0.047 ± 0.03
	Minimum	0.010	0.014	0.016	0.012	0.015	0.010
	Median	0.038	0.032	0.030	0.031	0.045	0.037
	Maximum	0.083	0.101	0.167	0.216	0.150	0.216
Hg	Mean±SD	0.36 ± 0.08	0.72 ± 0.49	0.25 ± 0.09	0.12 ± 0.10 (b)	0.07 ± 0.02 (c)	0.18 ± 0.24
	Minimum	0.24	0.091	0.033	0.041	0.053	0.033
	Median	0.37	0.55	0.27	0.083	0.065	0.086
	Maximum	0.45	1.80	0.43	0.41	0.11	1.80
Ni	Mean±SD	0.014 ± 0.011	0.056 ± 0.092	0.020 ± 0.014	0.030 ± 0.043	0.040 ± 0.043	0.035 ± 0.047
	Minimum	0.007	0.004	0.005	0.004	0.006	0.004
	Median	0.011	0.015	0.015	0.018	0.024	0.018
	Maximum	0.033	0.31	0.049	0.29	0.23	0.31
Pb	Mean±SD	0.048 ± 0.014	0.087 ± 0.099	0.094 ± 0.090	0.089 ± 0.098 (d)	0.18 ± 0.14	0.12 ± 0.12
	Minimum	0.034	0.034	0.030	0.008	0.017	0.008
	Median	0.044	0.056	0.059	0.059	0.18	0.07
	Maximum	0.070	0.39	0.39	0.44	0.86	0.86

weight). The estimated *per capita* consumption in the EU in 2015 was 2.77 kg tuna (EUMOFA 2017). Arsenic is present predominantly in the organic forms of arsenobetaine, arsenocholine, monomethylarsonic acid and dimethylarsinic acid. The toxicity of As compounds depends on the chemical form: inorganic As is much more toxic than the organic form (Hindmarsh and McCurdy 1986; Sirot et al. 2009). According to EFSA (2014a), fish and other seafood represent a problem when trying to derive the amount of inorganic arsenic from total arsenic because the ratio may depend on the seafood type (Cullen and Reimer 1989; EFSA 2009a), and the relative proportion of inorganic arsenic tends to decrease as the total arsenic content increases. In tuna, arsenobetaine is the dominating arsenic compound (Larsen et al. 1993) while toxic inorganic arsenic is present at lower concentrations. The CONTAM panel considered the average amount of inorganic arsenic in fish to be 0.1–3.5%. With a conservative approach, we decided to consider inorganic arsenic as 10% of the total arsenic and the highest of the mean and median values, 1.24 and 1.06 mg kg^{-1}, respectively, of total arsenic in tuna. Applying the above formula, the EDI of As is 0.016 μg kg^{-1} day^{-1} which is 19 times lower than EFSA $BMDL_{05}$ related to cancer of the skin, lungs and bladder, and skin lesions (0.3 μg kg^{-1}) (EFSA 2014a). Cd was detected in all samples analysed, with a concentration range 0.006–0.034 mg kg^{-1}, always lower than MLs set by European Commission 1881/2006. Median and mean had the same value of 0.014 mg kg^{-1}, and EDI of Cd calculated as above would be 0.0017 μg kg^{-1} b.w. This value is 210 times lower than TWI of 2.5 μg kg^{-1} b.w., considered on a daily base (i.e. divided by seven). Cr was in almost all samples investigated with a concentration range 0.01–0.22 mg kg^{-1}. The EDI calculated on the mean (0.047 μg g^{-1}), would provide a Cr intake of 0.0089 μg kg^{-1} day^{-1}, about 33700 times lower than TDI (300 μg kg^{-1} day^{-1}). Cr VI has not been evaluated due to its very low presence in the food (EFSA 2014b). The presence of mercury in tuna requires further comment. Areas 57 and 71 show significantly lower concentrations than other zones; the Mediterranean Sea (Area 37), however, while not showing differences between zones 27 and 51, provided the highest concentration by far of Hg and the highest median. This fact is likely to be due to the different number of samples from different areas. Three red tuna samples from the Mediterranean Sea, respectively, from Sicily (1.29 mg kg^{-1}), the Adriatic Sea (1.19 mg kg^{-1}) and Cyprus (1.80 mg kg^{-1}), exceeded the MLs set by the EU at 1 mg kg^{-1}. Our results agree with other studies conducted on tuna in the Mediterranean region where the concentrations of Hg were 0.12–3.23 mg kg^{-1} (Storelli and Marcotrigiano 2001) and 0.49–1.81 mg kg^{-1} (Srebocan et al. 2007). In tuna muscle tissues organic Hg is between 75%-100% of total Hg (Storelli et al. 2005). Based on the worst hypothesis, i.e. Hg was totally methylmercury, the EDI calculated on the mean (0.18 μg g^{-1}) content, would provide a Hg intake of 0.0021 μg kg^{-1} day^{-1}, about 88 times lower than TWI (1.3 μg g^{-1}) expressed as total Hg. Ni was detected in all tuna samples. The concentration range was 0.008–0.86 mg kg^{-1}. Considering the mean value, an average consumer would be exposed to 0.0042 μg kg^{-1} day^{-1} that is about 670 times lower than the TDI value of 2.8 μg kg^{-1} body weight, calculated by EFSA (2015). The acute toxicity of Ni plays a major role, as systemic contact dermatitis is a frequent adverse effect in nickel-sensitive individuals exposed to this metal through food. A 300 g serving of the most contaminated tuna would supply (0.31 x 0.3/60) = 1.6 μg kg^{-1} body weight to a 60 kg consumer, that is an amount higher than the $BMDL_{10}$ of 1.1 μg kg^{-1} body weight. Considering the recommended minimum value of 10 for the margin of exposure (MOE), the value considered of no concern would be 0.11 μg kg^{-1} body weight. The calculated concentration of Ni in tuna in a single meal that should not lead to the limit being exceeded is 0.022 mg kg^{-1} muscle; 85% of our samples had a Ni concentration higher than this calculated value (EFSA 2015). A risk of contact dermatitis through tuna intake is therefore present, even if lower than that observed in mussel and clams (Chiesa et al. 2018). Food is the main route of exposure of humans to Pb and cereal products contribute most to dietary exposure. Eleven analysed samples exceeded the MLs (0.30 mg kg^{-1}) with a range concentration 0.30–0.86 mg kg^{-1}. Ten of them were yellow tunas from Pacific FAO areas 57 and 71, while the one presenting the lower

concentration was a red tuna from Sicily. The comparison between zones showed a significant difference between FAO areas 57 and 71, which has a statistical significance due to similar numbers in the groups (Tables 1 and 3). The mean Pb concentration found in tuna samples was 0.12 mg kg^{-1}. An average consumer would, therefore, take in 0.014 μg kg^{-1} day^{-1}, an amount 45 times lower than the lower reference point referred to adults ($BMDL_{10}$ = 0.63 μg kg^{-1} day^{-1}). A study (Teuschler 2013) on Italian food consumption patterns in the '90s reported that fish consumption by children is about 65% that of adult consumers. If the weight of 16 kg for a 4-year-old child and the above-reported intake are accounted for, daily intake results in 0.037 μg kg^{-1} day^{-1}, a value 13 times lower than the $BMDL_{01}$ value of 0.50 μg kg^{-1} day^{-1} for developmental neurotoxicity in infants and children. This value could pose some concern if lower ages, and the intake of other foods are considered. In fact, cereals and cereal-based products, potatoes, leafy vegetables and tap water are the main contributors to Pb exposition (EFSA 2010) and tuna seems to contribute significantly to the health-based guidance value.

Evaluation of the hazard index

Metals and As in tuna can share some toxicological effects and evoke a dose addition that results in a *Total Dose*, i.e. the dose of each toxic agent with similar effects. Therefore, we calculated the Hazard Index (HI), i.e. the sum of more than one Target Hazard Quotients (THQ) shared by the different chemicals studied. Firstly, the THQ, i.e. the ratio of the estimated exposure to each substance and the level with no adverse effects, were evaluated as THQ = daily intake/RfV for each compound, for the different critical effects specified by EFSA. To calculate the HI, the following equation was used: $HI = \Sigma_{i=6}$ Estimated $intake_i$ $/RFV_i$, where, RfV_i is the Reference Value, that is the human daily intake of the substance i [TDI, TWI or BMDL] and the Estimated Intake, evaluated from annual consumption, is in the same units as the RfVi (Teuschler 2013). The RfVi were the reference doses indicated by EFSA (2009a, 2009b, 2010, 2012, 2015)), reconsidered on a daily base when necessary. All the HIs were much lower than one, indicating that only a negligible health hazard could derive from the ingestion of tuna, at least for the chemicals studied (Table 4). The HI for the 95th percentile consumers was also calculated based on previous studies (Leclercq et al. 2009; Chiesa et al. 2018), that indicated an estimated fish intake ratio of 3.65 for higher versus average consumers. Accounting for this value an EDI for the higher consumers was calculated and shown in Table 4. For this group of population, too, tuna is a negligible source of exposure for the chemicals studied. Finally, this work shows low risks for the health of average consumers. All the HIs were much lower than one, indicating that only a negligible health risk could derive with the intake of tuna from the chemicals studied. There is some

Table 4. Hypothetic target hazard quotient (THQ) and hazard index (HI) values for estimated daily exposure to the studied elements via tuna at mean concentrations detected. All the reference values (RfV) are by EFSA. TWIs are recalculated and expressed on a daily base. As is reported as inorganic Arsenic and only Cr(III) is considered. EDI is the estimated daily intake.

RfV		BMDL	TWI	TDI	TWI	TDI	BMDL		
Element		As	Cd	Cr	Hg	Ni	Pb	HI	HI
EDI (μg kg^{-1})		0.016	0.0017	0.0089	0.0021	0.0042	0.014	Average consumers	95% consumers
THQ (RfV μg kg^{-1} day^{-1})	Skin/lung/bladder cancer; skin lesions	0.053 (0.3)						0.053	0.19
	Reproduction/ Development			0.000030 (300)		0.0015 (2.8)		0.0015	0.0055
	Developmental neurotoxicity				0.011 (0.19)		0.028 (0.5)	0.039	0.14
	Blood pressure				0.011 (0.19)		0.0093 (1.5)	0.020	0.073
	Kidney		0.0048 (0.36)				0.022 (0.63)	0.027	0.099

concern about a cancer risk evoked by Pb and Cd. The evidence for the carcinogenicity of Pb in humans, and human exposure through food are not however considered sufficient to represent a risk (EFSA 2015). IARC (2012a) states that the evidence of Cd as a human carcinogen is sufficient, based on professional exposure and lung cancer but not all recent data associate Cd and cancer at low dietary intakes (Åkesson et al. 2014). The health risk assessment should, therefore, consider Cd for this toxic effect, if more unambiguous data become available.

ORCID

Antonio Procopio http://orcid.org/0000-0003-0225-033X

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