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Abstract

Seafood products are important sources of proteins, polyunsaturated lipids and phospholipids, and also of numerous micronutrients (vitamins and minerals). However, they may also present chemical contaminants that can constitute a health risk and that must be considered when evaluating the risk/benefit associated with consumption of this group of foods. Toxic metals and metalloids in seafood, such as mercury (Hg), cadmium (Cd), arsenic (As) and lead (Pb), are subjected to legislative control in order to provide the consumer with safe seafood. This review provides an exhaustive survey of the occurrence of these toxic metal(loid)s in seafood products, and of the risk resulting from their consumption. Consideration is given to aspects related to speciation, food processing and bioavailability, which are key factors in evaluating the risk associated with the presence of these toxic trace elements in seafood products.

Keywords

metals, metaloids, seafood, processing, speciation, bioavailability, exposure

1. Introduction

Seafood products are considered fundamental in our diet because of their high nutritional value. They are important sources of proteins, polyunsaturated lipids and phospholipids, and also of numerous micronutrients, group B vitamins, liposoluble vitamins A and D and minerals (phosphorus, potassium, sodium, calcium, magnesium, iron and iodine). However, they may also be carriers of biotic and abiotic contaminants. Among the abiotic contaminants, toxic trace elements are particularly important. Mercury (Hg), cadmium (Cd), arsenic (As) and lead (Pb) are the elements that have aroused greatest interest on the part of the organisations responsible for food safety and the scientific community. Numerous studies have been conducted to characterise contents and determine the risk associated with consumption of the food that contains them.

The toxicity of these trace elements has been extensively studied. The International Agency for Research on Cancer (IARC) has classified these elements or their chemical forms as carcinogenic [Cd compounds (IARC, 1993); inorganic As (IARC, 2004)] or possibly carcinogenic for humans [methylmercury CH_3Hg (IARC, 1993); inorganic Pb (IARC, 2006)]. Exposure to these elements at work has been linked to the appearance of certain pathologies, but there is less evidence concerning their toxic effects as a result of exposure through food. Chronic exposure to As through drinking water is associated with a greater prevalence of certain types of cancer, type 2 diabetes, cardiovascular and cerebrovascular problems, chronic obstructive respiratory diseases and non-carcinogenic skin disorders (hypo- and hyperpigmentation, palmar keratosis) (EFSA, 2009a). Some studies have shown the effect of CH_3Hg on the neurobehavioral function of children (aged 7--14) with prenatal exposure resulting from a maternal diet based mostly on seafood (Grandjean et al., 1997; Debes et al., 2006). The effect on cognitive capacity has also been demonstrated in child populations exposed to As through drinking water (Wasserman et al., 2004).

These data show the need to perform a strict control of the contents of these metals/metalloids in food and water that is consumed and to obtain a better characterisation of the processes that occur after ingestion with a view to seeking solutions to reduce exposure. The present review summarises existing information on the occurrence of these toxic trace elements in seafood products, the exposure resulting from consumption of these foods and the risk associated with it. Consideration has also been given to how the risk may be affected by factors such as processing, bioavailability or the presence of other compounds in the food matrix.

2. Contents and speciation of toxic trace elements in seafood

2.1. Mercury. Seafood products and mushrooms are the foods that have the highest Hg contents. Methylmercury (CH_3Hg) is considered to be the most abundant species of Hg in fish, although the percentage varies, depending on the type of product (59--100%; Cheng et al., 2009; EFSA, 2012; Maulvault et al., 2015). The percentage of CH_3Hg in shellfish is generally lower and it may not be the major species (20--43%; Maulvault et al., 2015).

The highest Hg concentrations are found in large predatory fish. The contents found in swordfish (0.031--4.9 mg/kg fresh weight, fw), tuna (0.60--1.47 mg/kg fw), shark (0.22--2.5 mg/kg fw) or marlin (1.77--12.7 mg/kg fw) (Monteiro and Lopes, 1990; Luckhurst et al., 2006; Branco et al., 2007; Torres Escribano et al., 2011) may exceed the legal limits. In its latest opinion on Hg, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) shows the range of concentrations in 6114 fish samples, which varies from 0.001 to 11.4 mg/kg fw, the maximum concentration being found in marlin (JECFA, 2011). Processed products derived from large predatory fish usually have much lower concentrations (<1 mg/kg) (Burger and Gochfeld, 2004; Yang et al., 2015). Other species of fish that generally do not exceed the legal limits, such as mackerel and sardines, may have higher values, depending on the area where they are caught. Specimens of these species collected from the Mediterranean Sea contain more Hg than those from other harvesting areas (Driscoll et al., 2013).

On the other hand, Hg contents in shellfish are relatively low, with concentrations that usually do not exceed 0.1 mg/kg fw: crustaceans: 0.022--0.091 mg/kg fw; molluscs: 0.007--0.037 mg/kg fw; cephalopods: 0.035--0.106 mg/kg fw (Zaza et al., 2011; Padula et al., 2016). In its summary of the information about Hg generated by various countries, JECFA shows that of the 1892 shellfish analysed only 20% had quantifiable values, ranging from 0.002 to 0.86 mg/kg fw, the highest values being found in crab. Various studies indicate that shellfish species contain CH_3Hg at concentrations lower than 0.5 mg/kg fw (JECFA, 2011; Cardoso et al., 2012; Padula et al., 2016).

Seaweed consumed by humans does not generally have substantial quantities of Hg (0.001--0.057 mg/kg dry weight, dw) (Almela et al., 2002; Besada et al., 2009). However, van Netten et al. (2000) reported high contents in seaweed from Japan and in Norwegian kelp tablets (0.24--1.08 mg/kg dw). Almela et al. (2002) found that the level of Hg in brown algae was higher than in red and green algae.

2.2. Cadmium. This metal is mostly found in its inorganic form in seafood, although it has been reported that after incorporation into tissues it associates with metallothioneins or other larger proteins (Luten et al., 1986). Although seafood products are not considered to be the largest contributors of Cd to the diet (EFSA, 2009b), some of them have high contents of this element, exceeding the legal limits. The concentrations in fish do not generally exceed 0.1 mg/kg fw (Kikuchi et al., 2002; Juresa and Blanusa, 2003; Voigt, 2003), but greater concentrations have been observed in canned products (Olmedo et al., 2013).

The highest contents in seafood are found in shellfish, especially in bivalves, in which concentrations may reach 10 mg/kg fw (Bendell, 2010). Bendell (2009) indicated that Cd concentrations in shellfish from the northwest coast of Canada are generally greater than values reported for shellfish from other parts of the world. This study reported high levels of Cd in Pacific oyster *Crassostrea gigas* (1.5--3.6 mg/kg fw) and four species of scallop, *Chlamys hastata*, *Chlamys rubida*, *Crassadoma gigantea* and *Patinopecten yessoensis* (5--9 mg/kg fw) (Bendell, 2009). The concentrations in crustaceans are lower than those determined in bivalves, but an exception is brown meat from crabs (0.8--62 mg/kg fw) (Noël et al., 2011), which comprises the edible parts of the crab, excluding the claw, leg and shoulder meat, and which may include the liver and gonads or parts thereof (WHO, 2012). The inclusion of the hepatopancreas may be the reason for the high content found in this edible portion of crab. Brown crabmeat derivatives (spreads, soups, pâtés, pastas, etc.) also present elevated contents of Cd, up to 8 mg/kg fw (Bolan and Bersuder, 2013).

With regard to algae, the concentrations found in dry seaweed range between 0.02 and 4.82 mg/kg dw (van Netten et al., 2000; Almela et al., 2002, 2006; Besada et al., 2009), *Hizikia fusiforme*, *Undaria pinnatifida*, *Porphyra* spp. and *Laminaria* spp. being the species that have the highest contents.

2.3. Arsenic. Seafood is the main source of total arsenic in the human diet and many species of this metal can be found in this type of food, the inorganic form being the most toxic. Arsenic concentrations in fish are usually lower than 5 mg/kg fw (EFSA, 2009a; Muñoz et al., 2000; Ruttens et al., 2012). Higher concentrations have been reported in certain samples to which consumers have access, such as Northeast Arctic cod (up to 100 mg/kg fw; Julshamn et al., 2012). Shellfish may also present high levels of total As concentrations, ranging between 1.2 and 26.2 mg/kg fw (Muñoz et al., 2000; Falcó et al., 2006; Sloth et al., 2008; Rangkadilok et al., 2015). Canned fish usually present total As concentrations not exceeding 1 mg/kg fw (Dos Santos et al., 2009; Olmedo et al., 2013).

Arsenobetaine (AB) is the predominant As species in fish and shellfish. The percentage in most fish and crustaceans is greater than 70%, while lower percentages have been reported in bivalves (24--52%) and fatty fish (26--110%) (Suñer et al., 2002). Arsenobetaine is considered practically innocuous; therefore, although the total As contents in seafood are high, consumption of these foods is not considered worrisome for consumers. Moreover, fish and shellfish are generally low in inorganic As (<0.2 mg/kg fw) (Muñoz et al., 2000; Uneyama et al., 2007; Julshamn et al., 2012; Copat et al., 2013). Some studies, however, have detected high concentration of the inorganic form in seafood from uncontaminated areas. In blue mussels from Norwegian fjords, Sloth et al. (2008) found concentrations of inorganic As up to 5.8 mg/kg fw, which represented 42% of the total As.

In marine seaweed, total As concentrations are also high, ranging between 1.84 and 149 mg/kg dw (Almela et al., 2006;; Rose et al., 2007; Khan et al., 2015). Arsenosugars are the predominant As compounds in marine algae (>70%) (Lai et al., 1997), an exception being the

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brown alga *Hizikia fusiforme*, for which inorganic As is the major form (47--80%; Almela et al., 2006), reaching 117 mg/kg dw (Almela et al., 2006).

2.4. Lead. Among the toxic trace elements reviewed, Pb is the least problematic one with regard to seafood, since the majority of the samples analysed in the published studies present Pb contents below the limit allowed by current legislations (table 1). Inorganic Pb is the predominant form in seafood, although some authors have found organic species, such as trimethyl Pb, in oyster tissue (Chen et al., 2014).

In fish, concentrations ranging from 0.013 to 0.5 mg/kg fw have been detected in uncontaminated areas (Sepe et al., 2003; Has-Schön et al., 2006; Medeiros et al., 2012; Taweel et al., 2013; Chahid et al., 2014; Morgano et al., 2014). Andreji et al. (2006) found an unusual amount of Pb in roach (34.59 mg/kg fw) in a sample collected in the river Nitra (Slovakia), where heavy metal contamination has been reported. In shellfish, the range of Pb contents varies from 0.003 to 0.77 mg/kg fw (Falcó et al., 2006; Sivaperumal et al., 2007; Whyte et al., 2009; Guérin et al., 2011; Kalogeropoulos et al., 2012; Copat et al., 2013; Zaza et al., 2015). In a study conducted in industrial areas in Spain, Besada et al. (2011) found high amounts of Pb in two samples of wild mussels (*Mytilus galloprovincialis*), up to 3 mg/kg fw.

In a study that analysed 12 species of canned seafood from Spanish markets, Olmedo et al. (2013) showed that canned samples of albacore tuna, mackerel, octopus and squid did not present any detectable amount of Pb. Cockle and mussel presented the highest amounts of this element, 0.97 and 1.3 mg/kg fw, respectively. Tahán et al. (1993) also found higher Pb contents in canned samples of mussels and common cockles marketed in Venezuela. Similar amounts of

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Pb were found in canned fish from Ghana and Saudi Arabia (<0.03--1.44 µg/g fw), canned sardine being the sample with the highest contents (Ashraf et al., 2006; Okyere et al., 2015).

Seaweeds and derivatives present Pb levels similar to those of other fishery products. In Spain, values between <0.05 and 2.44 mg/kg dw have been found, the highest amount being observed in the brown seaweed *Undaria pinnatifida*. *Hizikia fusiforme*, *Palmaria palmata* and seaweed salad also presented high values (2.06, 1.52 and 1.35 mg/kg, respectively) (Almela et al., 2006; Besada et al., 2009). Khan et al. (2015) reported slightly lower values of Pb in seaweeds from South Korea (0.032--0.988 mg/kg dw).

3. Legislation

Metal and metalloid contents in seafood are subject to control by the health authorities, which are trying to reduce this form of exposure to contaminants. The Codex Alimentarius recommends maximum levels of toxic trace elements, which are often used to establish national legislation. Table 1 summarises the main current legislation on Hg, Cd, As and Pb in seafood. Maximum levels consider the concentration of the chemical in the food and the amount of the food consumed. Therefore the limits for a metal(loid) can vary depending on the type of seafood (for example, between 0.5 and 2 mg/kg of Cd, depending on whether the samples are fish, bivalve molluscs, cephalopods or crustaceans), and sometimes they are defined for certain seafood species (for example, the EU and China establish specific maximum levels of Cd for swordfish and anchovy).

Speciation of As and Hg, which is crucial for evaluation of the risk associated with consumption, is not considered by all legislations. For As, seafood contains mostly organic arsenic species considered harmless, and therefore the total As content is not useful for risk estimation. Consequently, most countries do not establish limits for total As in seafood. It is the limitation of inorganic As that permits adequate control of the risk. Only Australia, New Zealand and China limit this species in seafood products, the Chinese legislation being much more restrictive. With regard to Hg, the Codex Alimentarius recommends a maximum level of CH_3Hg in fish, although only China legislates for this species of mercury, indicating that it is only necessary to analyse it when the total Hg level exceeds the maximum level for CH_3Hg. As can be seen in Table 1, the maximum contents permitted do not differ whether total Hg or CH_3Hg is limited, as organic mercury is the major species in seafood. It would be advisable for most legislation to take speciation into account in future years. That would increase the protection of the consumer and benefit the fisheries sector. In order to do so it would be necessary for countries to have a) validated analytical methods for analysis of the chemical species of interest and b) knowledge of the baseline of that chemical species in seafood products. Most countries have not started working on this task.

4. Dietary exposure through seafood consumption

Total diet studies (TDS) and evaluation of the intake of populations with extreme consumption or populations living in contaminated areas have been used to determine the main dietary sources of these elements and their chemical forms and to identify population groups at risk.

4.1. Mercury

Seafood is the main pathway of dietary exposure to Hg, specifically to CH_3Hg. For the European population, tuna, swordfish, cod, whiting and pike are major contributors to CH_3Hg

dietary exposure in adults, while the same species and hake are the most important sources for children (EFSA, 2012).

In the National Health and Nutrition Examination Survey (USA) carried out in 1999 and 2000, Mahaffey et al. (2004) estimated consumption of CH_3Hg for 1709 female participants who provided 30-day dietary recall and 24-hour records. Based on variability in quantity and species of fish and shellfish consumed and using an average Hg concentration for each fish/shellfish species, the authors estimated a mean Hg intake of 0.14 μg/kg body weight (bw)/week. Dabeka et al. (2003) estimated a mean dietary Hg intake of 0.154 μg/kg bw/week for two Canadian cities in the period 1998--2000, all intakes were well below the provisional tolerable weekly intake (PTWI) proposed by JECFA for CH_3Hg (1.6 μg/kg bw) (JECFA, 2011). EFSA (2004) shows national average Hg exposures from seafood ranging between 1.3 μg/week (the Netherlands) and 97.3 μg/week (Portugal), corresponding to <0.1 to 1.6 μg/kg bw/week (assuming a 60 kg bw for adults).

EFSA's latest report on Hg indicated that intake of seafood products may present a risk for certain population groups in Europe, because the 95th percentile dietary exposure was close to or above the PTWI for all age groups and high fish consumers may exceed the PTWI by up to six-fold (EFSA, 2012). Iwasaki et al. (2003) showed Hg intakes from seafood (geometric mean: 1.5 μg/kg bw/week) close to the PTWI in 154 mothers residing in Akita (Japan). Various organisations have issued recommendations to limit consumption of some seafood products in susceptible populations (pregnant women, breastfeeding women and children) (European Commission-Health and Consumer Directorate, 2004; Health Canada, 2008; AECOSAN, 2011a; EPA-FDA, 2014).

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Intake of Hg also increases in areas where there is contamination by Hg which reaches the food chain, especially large sea animals. This is the case of the Inuit communities living in Nunavut in the Eastern Arctic, an area characterised by anthropogenic Hg contamination due to considerable mining activity. The various age groups studied presented CH_3Hg intakes (6.3--8.0 µg/kg bw/week) that substantially exceeded the intake recommended by JECFA, local seafood products being the main contributors to this intake (Chan et al., 1995). According to a study by Tian et al. (2011), for the child population, beluga muktuk (33%), narwhal muktuk (26%), ringed seal liver (15%), fish (11%) and ringed seal meat (5%) were the major dietary Hg sources, accounting for 90% of total Hg intake.

4.2. Cadmium

Dietary exposure to Cd takes place mainly through intake of products of plant origin (cereals, vegetables, nuts, pulses), but seafood products, especially shellfish, can also make a substantial contribution to the diet. In Europe, fish and shellfish provide approximately 18% of total Cd to the diet of the adult population, similar to the percentage contributed by cereals, the greatest contributors (22%) (EFSA, 2009b). The Spanish Agency for Food Safety and Nutrition (AECOSAN) reports that fish and shellfish are the main dietary sources of Cd for the Spanish population (AECOSAN, 2011b).

It is estimated that regular consumers of bivalve molluscs have higher dietary Cd exposures (4.6 µg/kg bw/week) than the mean of the European population (2.3 µg/kg bw/week) (EFSA, 2009b). Sirot et al. (2008) confirmed this, evaluating exposure to Cd in a French population with high consumption of seafood products. The 50th percentile dietary Cd exposure ranged between 0.6 and 3.4 µg/kg bw/week, and a substantial part of the population exceeded the tolerable weekly intake (TWI) of 2.5 µg/kg bw established by EFSA's CONTAM panel (EFSA, 2009b). In that study, the main seafood contributors to total Cd exposure were crab (26%), shrimp (25%), whelk (8%), calico scallop (8%), canned anchovy (6%) and great scallop (6%).

4.3. Arsenic

The As content in seafood products is so much greater than in other foods that their contribution to As intake is very significant, even for populations whose consumption of seafood is not high. For example, both in Chile, with a low consumption of seafood (33.1 g/day) and in the Basque Country (Spain), with one of the highest consumptions of these products (89 g/day), seafood is the food that contributes most As to the diet (Muñoz et al., 2005).

Data of total As intake through consumption of seafood provided by TDS are numerous. Among the most recent values are those provided by the (23rd) Australian TDS, in which the fish food group contributed 32--41% of total As exposure for all age groups (mean dietary exposure: 0.42--1.4 µg/kg bw/day) (ATDS, 2011). A similar percentage was estimated in the Japanese population (32%), in which consumption of the brown seaweed *Hizikia fusiforme* also contributed very significantly to total As intake (28%), estimated as 170 µg/day (Sawada et al., 2013). The latest TDS (2007) published in Canada estimated a mean As intake of 0.97 µg/kg bw/day, mostly provided by seafood products (Health Canada, 2013). EFSA used data provided by 19 European countries to calculate total As intake in this region, in which seafood provided a daily intake of 0.52 µg/kg bw (EFSA, 2009a). In the USA, the TDS carried out by the FDA between 1991 and 1996 estimated that fish accounted for 80% of As intake for all population groups except infants (total As intake: 24--72.1 µg/day) (Egan et al., 2002).

Total As intake has no toxicological significance because the reference value has always been established for inorganic As. Most of the investigations and TDS do not quantify inorganic As and they estimate intake of this form of arsenic by assuming that a certain percentage of the total As in seafood is inorganic. This percentage, found by means of experimental studies, is variable but rarely exceeds 20% for seafood from uncontaminated areas (Muñoz et al., 2000; Leufroy et al., 2011). As far as we know, only the TDS for Australia (ATDS, 2011), Japan (Kayama et al., 2013), Chile (Muñoz et al., 2005) and the Basque Country in Spain (Muñoz et al., 2000) analyse inorganic As.

When the intake is estimated as inorganic As, the studies coincide in indicating the very small contribution that seafood products make to total intake of this form of arsenic (≤1%). Exceptions are the percentages estimated in Spain and Italy (5%--10%; EFSA, 2014). Very variable intakes have been reported, possibly because of the species of fish consumed by the various populations: 0.006 µg/kg bw/day in France (Leufroy et al., 2011) to 0.23 µg/kg bw/week in the Basque Country, Spain (Urieta et al., 2001). These intakes of inorganic As from seafood products are very far from the reference value proposed by EFSA ($BMDL_{0.1}$: 0.3--8 µg/kg bw/day; EFSA, 2009a) and JECFA ($BMDL_{0.5}$: 2--7 µg/kg bw/day; JECFA, 2011). In countries such as Japan and Korea the habit of eating certain algae increases inorganic As exposure. In fact, some agencies connected with food safety have issued recommendations to limit consumption of the brown seaweed *Hizikia fusiforme* because of its high inorganic As content (Canadian Food Inspection Agency; Food Standards Agency, UK). EFSA (2014) adverts also about this type of seaweed and also indicates that it could be found in food supplements.

4.4. Lead

Foods with high Pb contents (offal products, honey, crustaceans and molluscs, chocolate) are not the ones that contribute most to Pb intake. In the UK, the 2006 TDS showed that the bread and other vegetables group (17%) and beverages (16%) made the greatest contribution to Pb dietary exposure. The contribution pattern found in the UK is repeated in other countries and often the contribution of the seafood group to Pb dietary exposure is less than 2% (EFSA, 2010). The contribution made by seafood products is higher in China (9%) and Korea (31%).

Most countries have significantly reduced dietary exposure to Pb from food in the last two decades, and this effort has also affected seafood products. For example, in France the first TDS showed a Pb intake from shellfish in adults of 0.26 µg Pb/kg bw/day (Leblanc et al., 2005), whereas the value decreased to 0.005 µg Pb/kg bw/day in the second French TDS (Arnich et al., 2012).

5. Effect of processing on toxic trace element contents in seafood

Although it has been known for some time that the concentration of a contaminant in a food may be altered by processing, most evaluations of the risk associated with ingestion of seafood products are performed on the product as sold or captured (Cardoso et al., 2010, 2012; Liang et al., 2011; Hu et al., 2015). In some cases there have been proposals to make exposure estimates by using correction factors obtained from studies of the effect of processing, but this practice is not very widespread, possibly because of the numerous uncertainties involved.

Most studies on the effect of processing on the contents of the toxic elements considered in this review refer to canning and home cooking. There are no data indicating whether some other kind of processing such as freezing/thawing or preservation processes such as salting or preparations as surimi affect the final concentration of the element or its chemical form.

5.1. Mercury

Studies conducted on the effect of home cooking indicate that generally this process does not substantially alter the concentration of Hg. Morgan et al. (1997) showed that the most usual treatments (pan-frying, deep-frying, baking and boiling) produced a slight increase in total Hg contents (1.1 to 1.8 times), which, according to the authors, was caused by weight (moisture and fat) loss. They also demonstrated that the incorporation of lemon juice in the cooking process did not have any effect on the quantity of Hg. A recent study by Schmidt et al. (2015) also indicated that the cooking treatment (boiling, frying and roasting) did not affect the chemical form of Hg initially present in the raw fish.

The effect of canning on Hg contents has also been evaluated. Rasmussen and Morrissey (2007) showed that the average concentrations of total Hg in albacore tuna samples ranged between 0.09 and 0.24 mg/kg, while the contents after canning varied between 0.10 and 0.33 mg/kg, indicating that there were no substantial changes in Hg concentration during the canning process. Burger and Gochfeld (2004) reported that the fluid in which tuna was canned did not contain substantial quantities of Hg, which confirms that solubilisation of Hg from the food during the canning process does not take place.

5.2. Cadmium

Studies on canned seafood products show that this kind of processing produces an increase in the concentration of Cd. Galitsopoulou et al. (2012) evaluated Cd contents in all the steps of canning sardines and anchovies and came to the conclusion that the decisive step in the concentration of Cd was the steam-roasting process prior to canning. Canning of cephalopods produces very substantial increases (up to 500%) in the case of mantle. According to Galitsopoulou et al. (2009), this may be a result of the heat treatment applied to the product, which causes a loss in weight, and of the handling of the product to separate the mantle, with a consequent migration of the metal present in the visceral portion. They also showed that this process of redistribution of Cd during processing of cephalopods was related to metallothioneins (MTs), as these proteins were highly correlated with Cd contents in the preparation (Galitsopoulou et al., 2013). In raw squid, MTs were more abundant in viscera than in mantle, which was in agreement with Cd distribution. After canning, the quantity of MT decreased in viscera and increased in mantle, as also occurred with Cd.

Cd contents vary during home cooking, depending on the type of cooking process and the conditions in which it is applied (Wang et al., 2014; Galitsopoulou et al., 2013). To some extent the variation is related to product weight loss or to a possible solubilisation of Cd to the liquid used for cooking or exuded by the cooked product. Valadez-Vega et al. (2011) showed another possible source of variation during cooking, transfer of the metal to the food from the handcrafted glass-clay containers used for cooking. Their study was not conducted with seafood products, but it showed that migration can take place in any pH range and with foods of various kinds, so it is possible that it can be extrapolated to seafood products.

5.3. Arsenic

Cooking can produce a concentration or a loss of this metalloid for the same reasons as those given for the other elements (Devesa et al., 2001a). A noteworthy point is the substantial elimination of As, mainly inorganic As, that takes place during preparation and cooking of seaweed. Hanaoka et al. (2001a) showed that washing and soaking before cooking removed about 32 to 60% of the As contents in *Hizikia fusiforme*. The cooking treatment also brings about a reduction of total As (30--43%) and of its inorganic form (46--50%) in this seaweed (Laparra et al., 2004). However, the concentrations of inorganic As in the ready-to-eat product are still high from a toxicological viewpoint.

The high temperatures applied during cooking can produce changes in the chemical forms of this metalloid. Devesa et al. (2001b) showed that high temperatures could bring about decarboxylation of AB, giving rise to tetramethylarsonium ion (TMA^+) and trimethylarsine oxide (TMAO). They also demonstrated that this transformation takes place during the cooking of seafood products and that it depends on the temperature that the product reaches and on the duration of the treatment (Devesa et al., 2001c). In extreme conditions, which are not usual in home cooking, inorganic As may be generated from AB (Hanaoka et al., 2001b). Furthermore, if the cooking water is contaminated with inorganic As, a situation that exists in certain parts of the world (Díaz et al., 2004), this can also produce a change in the speciation of the seafood product because it brings about an increase in the inorganic form, which means an increase in the risk associated with ingestion of the product.

There are few studies on the effect of other kinds of processing on As contents in food. Vélez et al. (1997) showed a migration of As from canned seafood products to the accompanying liquid, which could reach concentrations of 4 mg/kg, AB being the predominant species (48--100%). Changes in arsenical forms during the canning process seem unlikely. According to Devesa et al. (2001b), transformation of the major species in seafood products takes place at

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temperatures above 150°C, which are not reached in the majority of food canning processes. Studies should be conducted to confirm this, evaluating the effect of the various steps of the process on the speciation of As.

5.4. Lead

The use of ceramic containers for cooking may produce an increase in the quantity of Pb present in food. This has also been shown in seafood products. For example, Disyawongs and Mukprasert (2005) showed a transfer of Pb in prawns cooked in ceramic containers. They also showed that frying in oil resulted in a higher Pb release from the vessel into the food compared with boiling. This increase is an isolated phenomenon, as the cooking of seafood products does not normally cause an increase in Pb contents (Perelló et al., 2008). There have even been reports of reductions in Pb concentrations in some kinds of cooking treatments. Ersoy et al. (2006) showed a reduction in sea bass fillets using baking and microwave cooking methods, indicating that baking could be a very suitable form of cooking because the decrease in the quantity of Pb was substantial. Similarly, Atta et al. (1997) reported a decrease in concentrations of Pb in *Tilapia nilotica* after baking.

Canning is a type of processing that can also modify the contents of Pb in seafood products. Galitsopoulou et al. (2012) reported a substantial increase (35--65%) in Pb contents in sardines and anchovies after they had been subjected to industrial-scale canning. They showed that it was the steam-roasting step prior to canning that caused the greatest increase in Pb, as also happened with Cd; however, for Pb the increases as a result of canning were smaller. On the other hand, in squid the effect of canning was very different. As thermal conditions cause moisture loss, an apparent Pb increase was expected in the processed samples; however, the results did not confirm this theory, possibly owing to Pb loss during treatment. In fact, in this case a considerable Pb concentration was detected in the brine post-canning, showing a clear tendency of Pb to migrate from the squid tissues to the brine (Galitsopoulou et al., 2013).

6. Bioavailability of toxic trace elements from seafood products. The risk associated with ingestion of a contaminant in food is mainly due to the entry of the contaminant into the systemic circulation, which is a consequence of its release from the food matrix during the gastrointestinal digestion and subsequent absorption across the gastrointestinal epithelium. The quantity that finally reaches the bloodstream (bioavailability) depends on a series of factors, such as the chemical form of the contaminant after its release from the matrix, its interaction with other components of the diet present in the lumen and competition for the mechanisms responsible for its absorption, among others. Most of the studies on bioavailability of toxic trace elements have been conducted with solutions of aqueous standards, and there is less information about this parameter in the case of food. Most of the studies with foods have concentrated on making an *in vitro* evaluation of the quantity of the element that is solubilised during gastrointestinal digestion, which is known as bioaccessibility, a parameter that represents the maximum amount of the element that is available for subsequent absorption. Studies on bioavailability or bioaccessibility in foods have shown that the food matrix has a great influence on the magnitude of the process (solubilisation/absorption), so it must be taken into consideration in order to obtain information closer to the reality.

6.1. Mercury

In vitro studies have shown that the quantity of Hg that is released from seafood products during gastrointestinal digestion differs considerably. The bioaccessibility of total Hg in fish is

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very variable (13--87%) (Torres-Escribano et al., 2010, 2011; He and Wang, 2011; Cano-Sancho et al., 2015). These variations have been observed even among samples of the same seafood species (38--83% for swordfish; Torres-Escribano et al., 2010). The major form in the bioaccessible fraction is CH_3Hg (>94%) (Torres-Escribano et al., 2010; Afonso et al., 2015; Cano-Sancho et al., 2015). The bioaccessibility reported for shellfish is higher (72--102%) (Calatayud et al., 2012; Cano-Sancho et al., 2015). The percentages of bioaccessibility decrease to a great extent, by as much as 60%, when seafood is cooked (Ouédraogo and Amyot, 2001; He and Wang, 2011; Torres-Escribano et al., 2011). Torres-Escribano et al. (2011) attributed this to alterations in the structural conformation of the fish muscle proteins produced by temperature, which could impede access of enzymes to the structures to which Hg is bound in the muscle. Also, the bioaccessibility of Hg from seafood decreases in the presence of food components (tannic acid, pectin, celluloses and lignin) (umpublished data) or in the presence of other foods, such as coffee, tea, psyllium, and wheat and oat bran (Ouédraogo and Amyot, 2001; Shim et al., 2009), possibly because of the formation of less soluble complexes.

The bioavailability of Hg depends largely on its chemical form. In laboratory animals and in humans it has been shown that the inorganic form is absorbed to a lesser extent (>20%) than CH_3Hg (<90%). There are few studies on bioavailability in seafood products, but they show the same trend as has been observed in aqueous solutions of standards. In seafood products, in which the greater part of Hg is in the form of CH_3Hg, absorption is high. Yanai and Sachs (1993) showed an Hg absorption percentage of 93 ± 5% in rats fed with diets based on fish meal prepared by grinding and mixing freeze-dried fish and shellfish tissues.

Intestinal absorption of Hg may be altered by some dietary components, although most of the studies on this aspect have not been conducted with foods. Janle et al. (2015) showed that the Hg present in swordfish was absorbed more efficiently in rats when it was administered together with green tea extract. The same effect was observed in humans fed with 2 daily fish meals and 6 cups of tea for 3 consecutive days (Canuel et al., 2006). The effect of fibre on the bioavailability of Hg is not so clear. Rowland et al. (1986) showed that the incorporation of 30% wheat bran in the diet of mice reduced the total Hg concentration in brain, blood and small intestine. They suggested that this was due to the presence of fibre, which binds Hg in the lumen and prevents its absorption. However, the presence of phytates, one of the major fibres in wheat bran (Stevenson et al., 2012), did not affect absorption of Hg from a fish meal diet in rats (Yanai and Sachs, 1993).

6.2. Cadmium

The bioaccessibility of Cd from seafood products is high (>50%) (Maulvault et al., 2011; Gao and Wang, 2014). Maulvault et al. (2011) conducted a detailed study on the various steps of the digestion process in crab meat and showed a high Cd bioaccessible fraction by the end of the digestive process (small intestine), reaching 84--95%. In the mouth, 6--13% of the total Cd content was already accessible, and 46--72% was solubilized in the stomach. The same study showed that cooking did not significantly affect the bioaccessibility of Cd, but other studies on other kinds of seafood products and with other cooking treatments show a very substantial reduction in Cd bioaccessibility as a result of cooking (Amiard et al., 2008; Houlbreque et al., 2011; Gao and Wang, 2014). On the other hand, the process of freezing does not have a marked

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effect on the bioaccessibility of this metal, as shown by Amiard et al. (2006) in a study conducted on bivalves.

It has been estimated that in humans there is low intestinal absorption (<6%) after oral administration of inorganic Cd (Elsenhans et al., 1997). Cadmium bound to MT, the form reported in tissues of seafood products, is absorbed to a lesser extent than Cd in the form of a salt (Sugawara and Sugawara, 1991). In fact, Vahter et al. (1996) observed very low absorption of Cd in non-smoking women after ingestion of shellfish diets. The components of the diet may also affect absorption of this metal. Diets deficient in Zn, Fe and Ca led to greater absorption and accumulation of Cd in rats (Reeves and Chaney, 2001, 2004), possibly because those minerals compete with Cd for transport mechanisms. This finding, obtained in animals dosed with aqueous solutions of inorganic Cd or fed with diets based on vegetables or rice, has not been studied in seafood products.

6.3. Arsenic

The release of As from seafood products during intestinal digestion varies, depending on the matrix. The bioaccessibility in seaweed ranges between 32 and 83% (Laparra et al., 2003; Brandon et al., 2014). A recent study showed that, of the arsenical forms present in seaweed, arsenosugars and inorganic As presented high bioaccessibility, whereas the release of dimethylarsinic acid (DMA) from the matrix during digestion did not exceed 36% (Brandon et al., 2014). Cooking significantly increased the quantity of total and inorganic As bioaccessibility in *Hizikia fusiforme* (Laparra et al., 2003), which is of great importance in view of the high inorganic As contents that this brown seaweed presents. Furthermore, a study by García Sartal et al. (2012) indicates that the forms of arsenic that are present in seaweed do not change during the digestive process.

The bioaccessibility of total As in fish and shellfish is high (58--89%) (Laparra et al., 2007; Maulvault et al., 2011; Cano-Sancho et al., 2015). Laparra et al. (2007) showed that the bioaccessibility of AB was very high in raw and cooked fish samples (107--115%), whereas the bioaccessibility of other organic forms of arsenic [DMA, monomethylarsonic acid (MMA), TMA^+ and TMAO] was lower.

In vivo studies show that intestinal absorption depends on the form of arsenic. In experimental animals, the absolute bioavailability of inorganic As is more than 75% (Freeman et al., 1995; Juhasz et al., 2006). The absorption reported for DMA varies between 80% in rodents (Vahter et al., 1984) and 33% in swine (Juhasz et al., 2006). Absorption of the more complex organic forms, AB and arsenocholine (AC), is almost complete in mice (Vahter et al., 1983; Marafante et al., 1984). Studies using food matrices (vegetables and rice) show a matrix effect that in most cases leads to a reduction in bioavailability. There are no data to indicate the quantity and forms of As that reach the bloodstream after ingestion of seafood products.

It has been found that in humans most of the As ingested with seafood is excreted rapidly without undergoing any metabolic process (Freeman et al., 1979; Lee et al., 1994). Elimination is also rapid for seaweed, but biotransformations have been observed. Ma and Lee (1998) showed a significant increase in DMA in urine after ingestion of yakinori and nori, which was not explained by the initial content of that dimethylated form in the food, indicating a transformation of arsenosugars into DMA. This is different from the situation in *Hizikia fusiforme*, in which the major species is inorganic As. There is only one study on excretion and accumulation of As after dosing mice with *Hizikia fusiforme* (Ichikawa et al., 2010). The authors showed that after 3 days of exposure the excretion ranged between 66 and 92% of the dose administered, and elimination in faeces (42--73%) was greater than in urine (10--30%). Data concerning the arsenic species in urine were not provided. For this seaweed the profile of metabolites in urine may be similar to that observed in population exposed to inorganic arsenic through the drinking water, where inorganic As is also the predominant species; however, the matrix may affect metabolism of the forms of arsenic, so studies are required to confirm the metabolism of the As present in *Hizikia fusiforme*.

6.4. Lead

There are few studies on the bioaccessibility of Pb in seafood products. Amiard et al. (2008) showed moderate bioaccessibility of Pb (18--52%) in shellfish samples. He and Wang (2013) reported that the bioaccessibility of Pb, like that of other elements (Cd and As) depends on the part of the shellfish that is analysed. Organs rich in muscle fibres and collagen, which are not easily digested by digestive enzymes, have lower bioaccessibility. Moreover, steaming and grilling reduce Pb bioaccessibility in shellfish samples by up to 40% (He and Wang, 2013; Gao and Wang, 2014).

A study of gastrointestinal absorption of lead chloride carried out on humans showed absorption rates ranging from 10 to 48% of the dose (Moore et al., 1979). In general, Pb uptake is markedly lower with consumption of meals than under fasting conditions in adults (Rabinowitz et al., 1980). Yannai and Sachs (1993) studied absorption of Pb in rats from diets based on seafood products and observed great variability (26-82%). They evaluated the effect of fibre on the absorption of Pb from the diets and showed that no reduction in absorption resulted

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from the diet containing phytates. Tong et al. (2015) showed a lower bioavailability (<10%) after dosing mice with cooked fish, which might suggest a reduction in the entry of Pb into the systemic circulation as a result of cooking the fish. Furthermore, oral bioavailability of the same Pb-containing seafood increased greatly in pregnant mice compared with non-pregnant mice (4% vs. 12%).

7. Risk associated with ingestion of seafood products with regard to toxic trace elements. In order to make a correct evaluation of the risk associated with ingestion of a food containing toxic trace elements it is necessary to take a series of factors into account. As has been shown throughout this review, quantification of a trace element in a foodstuff does not give an accurate idea of the risk associated with ingestion of it, because processing prior to consumption and the processes that precede gastrointestinal absorption may modify the quantity of the contaminant and the chemical form that reaches the systemic circulation. Furthermore, the contaminant forms part of a matrix and therefore there may be other substances that enhance or reduce its toxicity. At present there are few studies that make a suitable evaluation of the risk associated with ingestion of Hg, Cd, As and Pb from seafood products.

7.1. Mercury

In the case of Hg, some studies have been conducted to try to evaluate the risk associated with regular consumption of seafood products by measuring biomarkers of exposure such as total Hg in hair and blood. Brune et al. (1991) reviewed studies of populations exposed to Hg from various sources and found the highest values of the biomarkers (Hg in blood, blood cells and plasma) among seafood consumers in Greenland and Japan. In a review of 164 studies of Hg exposure in women and their infants from 43 countries, Sheehan et al. (2014) also found that

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biomarkers of CH_3Hg intake (total Hg in hair and blood) were of greatest health concern among various populations of seafood-consuming women and infants, specifically tropical riverine populations near gold-mining sites and traditional Arctic populations. They also highlighted the values of the biomarkers in coastal regions of south-eastern Asia, the western Pacific and the Mediterranean, the averages of which approached the reference values established by JECFA.

In its latest report on mercury in food, EFSA clearly indicated that exposure to CH_3Hg above the PTWI was of concern; however, if measures to reduce CH_3Hg exposure are considered, the potential beneficial effects of fish consumption should also be taken into account (EFSA, 2012). A recent review of evaluations of neurodevelopmental and cardiovascular outcomes associated with intake of Hg from seafood products indicated that the existing data were not conclusive and that this might be partly due to the fact that no account has been taken of other compounds present in the products which might be beneficial and may counteract the toxic effects of Hg, such as selenium (Se), vitamin E and polyunsaturated fatty acids (Choi et al., 2008). In fact, experiments performed on animals seemed to indicate that CH_3Hg toxicity is more closely related to the Hg/Se molar ratio than to Hg concentrations in blood and hair (Ralston et al., 2007). It has been demonstrated that Se may be able to antagonize the toxic effects of Hg (El-Demerdash, 2001). It has been suggested that long-chain n-3 polyunsaturated fatty acids in fish play a key role in protecting against cardiovascular diseases (Kris-Etherton et al., 2002), one of the outcomes of Hg exposure. Unfortunately, the great majority of cohort studies in this field have focused either on the risk of CH_3Hg or on nutrient benefits due to seafood consumption, but not both (Choi et al., 2008).

7.2. Cadmium

Studies on the risk associated with ingestion of this metal through seafood products have concentrated mainly on consumption of shellfish. Some shellfish from the northwest coast of Canada had higher Cd contents than those from other parts of the world (Bendell, 2010), and therefore official organisations issued recommendations to limit consumption of some of them (oysters, scallops). Subsequent evaluations of Cd intake due to regular consumption of these seafood products (3 units/week) indicated that the intake was very close to the level recommended by JECFA (Cheng and Gobas, 2007; Widmeyer and Bendell-Young, 2008). Cheng and Gobas (2007) identified groups for which regular consumption of shellfish from the northwest coast of Canada would represent a risk; they were women with low iron stores, people with renal impairment, smokers, children, and people who consume organ meats of game and wildlife which frequently contain high concentrations of cadmium. USDA (2008) also made an evaluation of the risk associated with ingestion of Pacific oysters from the U.S. West Coast and concluded that, assuming that consumers were not exposed to significant quantities of Cd from other sources, consumption of Cd in oysters from areas sampled in Washington was not likely to present a health hazard. However, if Cd intake via dietary sources other than oysters is taken into account, Cd intake may become a health concern.

McKenzie et al. (1986) made an evaluation of Cd intake and the associated risk in a population with a high consumption of buff oysters. They showed that there was a very high intake in the group of extreme consumers (≥ 6 dozen oysters/week); however, the increase in the level of Cd in blood was not very high (1.2 ng/mL), possibly because, as commented earlier, the bioavailability of Cd is relatively low in humans and also depends on the presence of other minerals (Zn, Fe, Ca), which are present in high levels in this kind of seafood. They also emphasised that they did not observe any medical problems, although they reported higher blood pressure in individuals who consumed more than two dozen oysters a week.

7.3. Arsenic

With regard to As, although the contents are high in most fish and fish products, the fact that the major form is AB means that there is no risk associated with intake of them (Borak and Hosgood, 2007). However, there are more reservations in the case of seaweed, especially the brown seaweed *Hizikia fusiforme*. Although this alga is particularly consumed in the Asian countries, it is also commercialised in Europe and can be found in restaurants, supermarkets and as part of food supplements of dietary fibre and/or minerals (EFSA, 2014).

Watanabe et al. (1979) evaluated the effects of ingestion of various *Hizikia* preparations (final arsenic concentrations: 9, 17 and 21 mg/kg) in rats during 37 weeks. They concluded that no pathological signs could be detected in any parameters (haematology, blood biochemistry and pathology of major organs and skin). A later study, conducted on rats dosed for 7 weeks with a diet containing 3% of *Hizikia fusiforme* powder (cumulative intake of total and inorganic As was 2.07 mg and 1.46 mg, respectively), also showed no changes in haematological parameters; however, significant but not very substantial modifications were observed in biochemical parameters such as alkaline phosphatase and inorganic phosphorus in plasma and there was a very high As concentration in most of the organs evaluated at the end of the exposure (Yokoi and Konomi, 2012). These studies indicate that consumption of these types of seaweed may not be harmful, but they must be treated cautiously because the work was done with rats, animals that, because of their metabolism, show less susceptibility to the toxicity of inorganic forms of As.

7.4. Lead

With regard to Pb, the studies conducted to evaluate the risk associated with ingestion of seafood products (Guéguen et al., 2011; Hu et al., 2015) have shown that in no case is the PTWI proposed by JECFA exceeded and that, in general, there are no seafood products of concern with regard to this metal.

8. CONCLUSIONS

The presence of toxic trace elements such as Pb, Cd, Hg and As in seafood products has traditionally been one of the objects of environmental or food safety studies. The abundant information generated in recent decades has made it possible to obtain baselines of contents, which are fundamental for the establishment of legislation (maximum levels in seafood) and for knowledge about human exposure to these contaminants as a result of consumption of seafood products. This control of contents and human exposure, which should become a routine activity for countries, must be accompanied by a willingness to face new challenges that could contribute to a truer evaluation of the risk/benefit associated with ingestion of seafood products, as commented on in this review.

The determination of CH_3Hg and inorganic As in seafood products by food control organisations, with all that this implies (development, validation and implementation of robust and economical analytical methods), is one of the priorities. A deeper study should also be made of the effect that cooking treatments or processing may have on these contaminants, the quantitative and qualitative (chemical species) changes that may take place, and the extent to which they may affect subsequent absorption and toxicity of the contaminant. The role of the diet in the absorption and metabolism of metals and metalloids conveyed by seafood should also be evaluated in detail, as it has been shown that some components of seafood products may have a protective effect.

Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

AB arsenobetaine

AC arsenocholine

AECOSAN Agencia Española de Consumo, Seguridad Alimentaria y Nutrición

BMDL benchmark dose level

Bw body weight

Dw dry weight

CH_3Hg methylmercury

DMA dimethylarsinic acid

EFSA European Food Safety Agency

FDA Food and Drug Administration

Fw fresh weight

JECFA Joint FAO/WHO Expert Committee on Food Additives

MMA monomethylarsonic acid

MT metallothionein

PTWI	provisional tolerable weekly intake
TDS	total diet studies
TMA^{+}	tetramethylarsonium acid
TMAO	trimethylarsine oxide
TWI	tolerable weekly intake

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Table 1. Maximum levels of contaminants in seafood products subject to legislation in various countries.

Arsenic (total)	**Maximum levels (mg/kg**	**Reference**
Fish protein	3.5	Canada, 2015
Arsenic (inorganic)	**Maximum levels (mg/kg**	**Reference**
Aquatic animals and their products	0.5	GB 2762-2012
Fish	2	FSANZ
Fish and their products	0.1	GB 2762-2012
Crustaceans	2	FSANZ
Molluscs	1	FSANZ
Seaweed	1	FSANZ
Foods with added algae for special	0.3	GB 2762-2012
Aquatic seasonings	0.5	GB 2762-2012
Fish seasonings	0.1	GB 2762-2012
Cadmium	**Maximum levels (mg/kg**	**Reference**
Fish	0.050-0.25	EU 488/2014
Bivalve molluscs	2	CODEX STAN 193-
	1	EU 488/2014
	2	FSANZ
Cephalopods	2	CODEX STAN 193-
	1	EU 488/2014
Crustaceans	0.5	EU 488/2014
Fish seasoning	0.1	GB 2762-2012
Lead	**Maximum levels (mg/kg**	**Reference**
Fish	0.3	CODEX STAN 193-
	0.3	EU 1005/2015
	0.5	FSANZ
Bivalve molluscs	1.5	EU 1005/2015, GB
	2	FSANZ
Cephalopods	0.3	EU 1005/2015
Crustaceans	0.5	EU 1005/2015, GB
Fresh and frozen aquatic animals	1	GB 2762-2012

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Aquatic products (excluding jellyfish	1	GB 2762-2012
Jellyfish products	2	GB 2762-2012
Algae and their products (excluding	1 mg/kg (as dry weight)	GB 2762-2012
Mercury (total)		
Fishery products and muscle meat of	0.5/1	EU 420/2011,
Crustacea	0.5	FSANZ
Molluscs	0.5	FSANZ
Methylmercury		
Fish	0.5	CODEX STAN 193-
Aquatic animals and their products	0.5	GB 2762-2012
Predatory fish	1	CODEX STAN 193-