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Review

Systematic review of arsenic in fresh seafood from the Mediterranean Sea and European Atlantic coasts: A health risk assessment

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ABSTRACT

Arsenic in the environment pose major threats to human health, and especially the inorganic form can result in adverse health effects. This review analyse papers from 2004 to 2017 on As in fresh fish and molluscs caught in the Mediterranean sea and the European coast of the Atlantic ocean allowing the identification of the marine area with a greater As bioavailability and in particular the identification of the European populations more exposed to In-As by consuming fresh seafood.

Results were separated on the base of the fishing site and the concentrations were reworked to assess the average daily intake to In-As as well as Target Hazard Quotient and Cancer Risk.

Overall, the greater availability in Tot-As concentration in the pelagic compartment found in the Mediterranean Sea is not present along the European coasts of Atlantic Ocean. Furthermore, only in the Mediterranean Sea, results highlighted significant differences between Tot-As concentrations in seafood subgroups.

In both areas, In-As concentrations showed the following trend: molluscs > pelagic > demersal with significant differences between subgroups.

The European populations more exposed to In-As from fish and molluscs are the French, Spanish, Italian and Greek, with particular regards to children of 3–6 years old, which should minimize the consumption of molluscs to avoid carcinogenic and non-carcinogenic risks.

1. Introduction

Arsenic (As) is a widespread metalloid element, presents both in organic (Org-As) and inorganic (In-As) form (Braman and Foreback, 1973). It is present in every environmental matrix (soil, water and air) due to natural causes (e.g. volcanic activity, mineral leaching and weathering) and anthropogenic sources (e.g. coal combustion, industrial exhaust) (Andaloro et al., 2012; Garelick et al., 2008). As is naturally available in minerals, i.e. arsenopyrite (FeAsS), realgar (As_4S_4), and orpiment (As_2S_3) (O'Day, 2006). Its extraction from mines and the conversion in the elemental form is not rare, due to its use in the metallurgical industry (for Lead and Copper alloys), and in the production of herbicide, fungicide, pharmaceutical and others (Leermakers et al., 2006; Manahan, 2002). The relatively frequent use of arsenic and its compounds in both industry and agriculture points to a wide spectrum of opportunities for human exposure. This exposure can be via inhalation of airborne As, contaminated drinking water, beverages, or from food and drugs. Recently international legislations (e.g. European legislation) decided to put down As emission from many products such as all herbicides and pesticides containing As compounds, with their product cancellation order and amendments to terminate uses (EPA, 2009; US EPA, 2000a).

In-As is known to be present in two oxidation states: Arsenite (As-III) and Arsenate (As-V). The balance between the two forms is various and matrix-dependent, in fact these species can undergo different modifications, depending on the environment in which the species are exposed to. Usually arsenate (As-V) is the most stable state in oxic water, while in reductive environment it is rapidly reduced into the more toxic form: As(III) (Cullen, 1989; O'Day, 2006). These modifications can occur by microbiological metabolism too (Kumari and Jagadevan, 2016). As(III) can be mono- and dimethylated to form organic compounds known as monomethylarsinic acid (MMA) and dimethylarsenic acid (DMA), which generally are considered to be of lower toxicity compared to In-As and occur in lower levels in aquatic ecosystems (Akter et al., 2005). In-As is generally more toxic and prevalent than organoarsenicals (Smedley and Kinniburgh, 2001).

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Moreover, As exists in other non-toxic organic compounds known as arsenosugars, arsenolipids and arsenobetaine (AsB). AsB, the major form of As in fish and most seafood, is not metabolised in humans, it is excreted unchanged, and it is widely assumed to be of no toxicological concern (EFSA, 2009; Sloth et al., 2005). Generally, these organic forms are considered safe for human consumption, contrary at the usual chemical behaviour of other organometalloid (i.e. mercury, more toxic in its organic form than the inorganic one) (O'Day, 2006).

Increasing concentrations of As in the environment pose major threats to human health, as exposure through inhalation, ingestion and skin contact can result in a multitude of adverse health effects (Bustaffa et al., 2014; Hubaux et al., 2013; Sage et al., 2017; Vimercati et al., 2017). Ingested In-As is largely metabolised and excreted in urine with a short half-time ranging from a few hours to two days, including arsenous (As-III) and arsenic (As-V) acids (together, In-As), MMA, and DMA, with typical ratios of 10–30% In-As, 10–20% MMA, and 60–80% DMA (Yusà et al., 2018).

A primary route of human exposure to As is through the oral consumption of contaminated groundwater sources (Ferrante et al., 2018; Huang et al., 2015), however, the intake of contaminated food products, such as fish and grains, is also a growing issue (Ferrante et al., 2017; Liao et al., 2018). It is estimated that daily we are exposed through ingestion of As contaminated food and water, within a range of 20–300 μg/day (EFSA, 2014a). To give just a few examples, results of a recently published market basket study conducted in a Polish adult population revealed an average daily intake of total As of 23.9 μg/day in women and 32.8 μg/day in men (Koch et al., 2016). An Italian study, which used a semi-quantitative food frequency questionnaire to assess the dietary habits of a representative sample of 719 individuals, reported an average daily intake of total As of 0.823 μg/kg of body weight (bw) per day in women (57.61 μg/day for 70 kg bw), and a total As of 0.684 μg/kg of body weight (bw) per day in men (47.9 μg/day for 70 Kg bw), in which fish and seafood are the third largest contributor to In-As exposure after cereals and beverage (Filippini et al., 2018). Among seafood, some species of seaweed, particularly the fucoids, are well-known accumulators of the metalloid arsenic (As) and with a consumption from two to three times a month, the contribution to cancer occurrence through the consumption of hijiki seaweed may not be negligible (Nakamura et al., 2008). With respect to food safety, consumption of 3 g/day of the seaweed could represent up to 15% of the respective Tolerable Daily Intakes (TDI) established by the WHO. The situation is especially alarming for intake of inorganic As from *H. fusiforme*, which can be three times the TDI established (Almela et al., 2006). Nevertheless, such exposure among European countries can be associated only with extreme seaweed consumers, such as those who follow a macrobiotic diet (Almela et al., 2006). Furthermore, most of edible seaweeds sold in Europe are imported from other countries, such as Japan, China, Korea and Chile, and it is difficult to find fresh seaweed in the fish market, which is the essential entry criteria for this study.

The concentration of Tot-As in seafood varies considerably both between and within species. As values typically reported are in the range of 3–15 mg As/kg wet weight (Conti et al., 2012; Copat et al., 2018; FSA, 2005; Julshamn et al., 2004; Sirot et al., 2009), till values ranging from 14.4 to 61.5 mg/kg wet weight in skate (*Raje* sp.) (Storelli and Marcotrigiano, 2000). Nevertheless, due to the lack of enough analysis on In-As in food commodities, maximum levels for As have only been set for rice and cereal derived products. In particular, Commission regulation (EU) 2015/1006 of 25 June 2015 amending Regulation (EC) No. 1881/2006 as regards maximum levels of In-As in foodstuffs, set limits in the range of 0.20–0.30 mg/kg wet weight for rice, husked rice, milled rice and parboiled rice, as defined in Codex Standard 198–1995, and a limit equal to 0.10 mg/kg wet weight for rice destined for the production of food for infants and young children.

International literature about Tot-As exposure risk assessment derived from seafood consumption for European population is relatively exhaustive (Baeyens et al., 2009; Bogdanović et al., 2014a; Cano-Sancho et al., 2015; Conte et al., 2015; Conti et al., 2012; Copat et al., 2013; Di Bella et al., 2015; Falcó et al., 2006; Gao et al., 2018; Guéguen et al., 2011; Llobet et al., 2003; Martí-Cid et al., 2007; Nadal et al., 2008; Núñez et al., 2018; Rodríguez-Hernández et al., 2016; Storelli et al., 2010; Storelli and Marcotrigiano, 2001). Only few authors conducted an In-As speciation, allowing a better assessment of the risk (Fontcuberta et al., 2011; Julshamn et al., 2012; Kalantzi et al., 2017; Maulvault et al., 2015; Perelló et al., 2014; Piras et al., 2015a,b; Sloth and Julshamn, 2008); For some species even season variations play a certain role (Copat et al., 2012), but some have linked these variations to spawning season, or more generally to life-cycle phases (Boyle et al., 2008).

The aim of this work was to evaluate the human health risks associated to the consumption of seafood species with high In-As levels caught from European coasts of Atlantic Ocean and Mediterranean coasts, through an intensive review of literature on In-As concentrations in edible tissues of fresh seafood, as well as the methodology applied for its determination, comparing Tot-As and In-As concentrations between the studied areas; the estimated daily intake to In-As derived from seafood consumption of representative adult general populations, living in the countries along the considered coastal environments; the development of seafood consumption limits, which could avoid the outbreaks of chronic systemic and carcinogenic effects due to oral exposure to In-As. This review will allow the identification of the marine area with a greater As bioavailability and in particular the identification of the European populations more exposed to In-As by consuming fresh seafood collected from local fish markets. Furthermore, our findings will also help to make more targeted choices of the seafood products sold at the large distribution.

2. Materials and methods

2.1. Selection of studies

We gathered studies from 2004 to 2017 on As concentration in marine species (demersal fish, pelagic fish and molluscs) destined to human consumption, dividing them in two groups based on the catching area, Mediterranean Sea and European Atlantic coasts (including North Sea considered a marginal sea of the Atlantic Ocean). We selected only research articles clearly indicating the analysis of fresh seafood collected in local fish market and never at the supermarkets.

We have collected a total of 25 research articles. Of these, only 7 applied the In-As speciation, 4 were conducted in the Mediterranean Sea (Fontcuberta et al., 2011; Kalantzi et al., 2017; Perelló et al., 2014; Piras et al., 2015a,b) and 3 in the European coasts of the Atlantic Ocean (Julshamn et al., 2012; Maulvault et al., 2015; Sloth and Julshamn, 2008).

Information about species, type of reporting weight concentration basis (i.e. wet weight basis or dry weight basis) (i.e., dry weight, d.w. or wet weight, w.w.), concentration of Tot-As and In-As, and area of sampling were put onto an Excel spread sheet. When speciation of In-As was missing, we calculated it based on the mean percentage of In-As reviewed for demersal fish, pelagic fish and molluscs.

After the data gathering, we converted all concentrations in mg/kg and, whenever data was given as d.w., it was adjusted for the w.w. based on the average water content of species: 81% molluscs, 72% for pelagic and 77% for demersal (FAO and SIFAR, 2001). Data for "Tot-As" and "In-As" are expressed as average of concentrations.

2.2. Statistical analysis

Statistical analysis has been conducted on SPSS software, version 20 (IBM, USA). ANOVA one-way was applied to compare mean concentrations of Tot-As and In-As between demersal fish, pelagic fish and molluscs within the Mediterranean Sea and the European coasts of

Atlantic Ocean. Then, we applied the Test-t for independent samples to compare mean concentrations of Tot-As and In-As between seafood categories within the two catching area.

2.3. Estimated daily intake

Concentrations reviewed were reworked to assess the estimated daily intake to In-As as well as the risk factors, Target Hazard Quotient (THQ) and Cancer Risk (CR). To assess the daily intake from As exposure by fresh seafood consumption we used data from Food and Agriculture Organization of the United States (FAOSTAT) database to obtain the value of annual average ingestion rate (IR) specific per seafood category and per country. At the moment, the previously reported provisional tolerable daily intake (PTWI) for In-As (2.1 μg/kg bw per day) is considered no longer health protective as the BMDL0.5 value was in the same range as the PTWI value (JECFA, 2018). Based on data from an epidemiology study conducted on a highly-exposed population, the In-As lower limit on the benchmark dose for a 0.5% (BMDL0.5), increasing incidence of lung cancer was calculated to be 3 μg/kg bw per day (range: 2–7 μg/kg bw per day), using a range of assumptions to estimate total dietary exposure of the study population to In-As from drinking water and food (JECFA, 2018). We thus calculated the estimated daily intake (EDI ng/kg bw per day) of In-As by seafood consumption as reported in a previous article (Conte et al., 2015) (Eq. (1)), comparing it with the BMDL0.5 suggested by WHO:

$$EDI = \frac{IR * C}{BW} \tag{1}$$

Where, IR is the ingestion rate (kg/pro-capita/day) specific per seafood category and country (FAOSTAT, 2017), C is the concentration of In-As (ng/kg w.w.) reviewed from fresh seafood of the European coasts of the Atlantic Ocean or of the Mediterranean coasts, and BW is the body weight (70 kg for adults) (US EPA, 2000b).

2.4. Risk-based consumption limits

Using guidelines provided by the United States Environmental Protection Agency (US EPA, 2000b), we have calculated As risk factors. We have assumed the ingestion dose of an average meal size suggested by EPA of 227 g for adults of 18–70 years and 114 g for children of 3–6 years. The revised studies do not indicate the effects of conservation, cooking and preparation methods which could affect the bioaccessibility of trace elements, with only some exceptions (Cano-Sancho et al., 2015; Fontcuberta et al., 2011). Nevertheless total As concentrations in seafood is generally unaffected by steaming and cooking and, its bioaccessibility between raw and cooked products remain the same (Alves et al., 2018; Cano-Sancho et al., 2015; Ersoy, 2011; Maulvault et al., 2012, 2011). At least, incorporation of bioaccessible As in the toxicological assessment reduces the risks compared to the whole contaminant levels (Maulvault et al., 2011), although future studies should assess if the inorganic fraction of As in these seafood species follows the same trend of total As (Alves et al., 2018).

THQ and CR are tools developed to assess non-carcinogenic and carcinogenic risk, and they have been calculated using the following formulae:

$$THQ = \frac{(EF * ED * MS * C)}{(RfD * BW * AT)} \tag{2}$$

$$CR = \frac{(EF * ED * MS * C * CSF)}{(BW * AT)} \tag{3}$$

in which EF is the Exposure Frequency (from 365 days/year for people who eat fish seven times a week to 52 days/year for people who eat fish once a week); ED is the Exposure Duration (for adults 18–70 years, children 3–6 years), MS is the meal size, C is the As concentration (mg/kg), RfD is the Oral Reference Dose (μg/g/day), BW is the Body Weight (70 kg for adults 18–70 years and 17.4 kg for children 3–6 years), AT is the Average exposure Time (equal to EF × ED) and CSF is the Cancer Slop Factor (μg/g/day of In-As trough oral intake).

For THQ a result lower than 1 means there is no adverse effect, but a value greater than 1 does mean there is define as the statistical probability to develop chronic systemic effects, but it doesn't provides a risk quantification. CR, in turn, is defined as the “cancer potency”. Since US-EPA assumes that carcinogens do not have safe thresholds, the CR is usually the upper 95% confidence limit on the linear term in the multistage model based on data obtained in an epidemiological study or a chronic animal bioassay (US EPA, 2000b). If CR results above Acceptable Lifetime Risk (ALR), equal to 1×10^{-5} (US EPA, 2000b), there is 1 chance over 100,000 that a person could develop cancer from the oral exposure to In-As.

3. Results and discussion

3.1. In-As speciation in seafood

We have collected a total of 25 research articles dealing with As concentration in seafood caught in the Mediterranean area and Atlantic Ocean area, belonging to demersal, pelagic and molluscs group species. Of these, only 7 applied the In-As speciation, 4 were conducted in the Mediterranean Sea (Fontcuberta et al., 2011; Kalantzi et al., 2017; Perelló et al., 2014; Piras et al., 2015a,b) and 3 in the European coasts of the Atlantic Ocean (Julshamn et al., 2012; Maulvault et al., 2015; Sloth and Julshamn, 2008).

In-As speciation has been conducted throughout the reviewed literature with hyphenated technique, e.g. HPLC-ICP/MS, HPLC-AA. Given the standard deviation found, Tot-As (mg/kg w.w.) varied in all the three analysed group species (demersal, 4.963 ± 5.28; pelagic, 5.9 ± 6.87; molluscs, 3.56 ± 3.33); the same variability was found for In-As (mg/kg w.w.) (demersal, 0.0082 ± 0.03; pelagic, 0.01 ± 0.02; molluscs, 0.08 ± 0.15). On the base of the speciation results we have calculated an In-As fraction for each seafood group (demersal = 0.14%; pelagic = 0.412%; molluscs = 2.37%); then we assessed these fractions to the studies in which it has not been conducted a speciation analysis (Andaloro et al., 2012; Bogdanović et al., 2014b; Cano-Sancho et al., 2015; Conte et al., 2015; Copat et al., 2013; Kalantzi et al., 2017; Martí-Cid et al., 2008, 2007; Martínez-Gómez et al., 2012; Minganti et al., 2010; Olmedo et al., 2013; Storelli and Marcotrigiano, 2004; Vieira et al., 2011).

3.2. Mediterranean Sea

Statistical analysis highlighted significant differences between Tot-As concentrations in seafood subgroups ($p < 0.05$) in the Mediterranean Sea. Overall, Tot-As concentrations bioaccumulated in these seafood show the following trend: pelagic > demersal > molluscs (Table 1). In particular, the post-hoc Tukey test revealed Tot-As concentrations in pelagic fish (6.466 mg/kg w.w.) significantly higher than molluscs (3.992 mg/kg w.w.) ($p < 0.05$); however there are not any other significant differences among subgroups.

In-As concentrations showed the following trend: molluscs > pelagic > demersal (Table 1) with significant differences between subgroups ($p < 0.001$). The post-hoc Tukey test revealed significant higher concentrations in molluscs (0.0977 mg/kg w.w.) versus pelagic and demersal fish (0.0251 and 0.0125 mg/kg w.w. respectively) ($p < 0.001$); there are not any other significant differences among subgroups.

In particular, in the demersal species the median Tot-As concentration is 3.520 mg/kg w.w. In this group species, the lowest Tot-As concentration is 0.025 mg/kg w.w., found in *Dicentrarchus labrax* in Muricia (Spain) area (Olmedo et al., 2013) and a maximum of 19.8 mg/kg w.w., found in *Mullus barbatus* caught in Porman (Spain) (Martínez-Gómez et al., 2012). In-As median value reported in literature for

Table 1
Descriptive statistics of Tot-As and In-As (mg/kg w.w.) of fresh seafood sampled along Mediterranean coast.

Mediterranean coasts			Tot-As	In-As(Results including recalculation)	In-As(Only literature data)
Demersal	Numbers of data		*46*	*46*	*19*
	Mean		5.059	0.0125	–
	Median		3.520	0.0037	0.0009
	S.D.		5.347	0.0383	–
	Min.		0.025	< loq	< loq
	Max.		19.80	0.2600	0.2600
	Percentiles	25	0.388	0.0002	–
		75	7.063	0.0129	–
Pelagic	Numbers of data		*79*	*79*	*18*
	Mean		6.466	0.0251	–
	Median		4.600	0.0177	0.0117
	S.D.		7.147	0.0289	–
	Min.		0.188	0.0008	0.0025
	Max.		52.41	0.2159	0.0390
	Percentiles	25	2.000	0.0083	–
		75	8.610	0.0322	–
Molluscs	Numbers of data		*41*	*41*	*20*
	Mean		3.992	0.0977	–
	Median		2.850	0.0549	0.0500
	S.D.		3.643	0.1738	–
	Min.		0.172	0.0024	0.0010
	Max.		19.06	0.9900	0.9900
	Percentiles	25	2.040	0.0418	–
		75	4.255	0.0920	–

Table 2
Descriptive statistics of Tot-As and In-As (mg/kg w.w.) of fresh seafood sampled along European Atlantic coasts.

European Atlantic coasts			Tot-As	In-As(Results including recalculation)	In-As(Only literature data)
Demersal	Numbers of data		*28*	*28*	*26*
	Mean		4.719	0.0013	–
	Median		2.550	0.0015	0.0015
	S.D.		5.269	0.0005	–
	Min.		0.066	< loq	< loq
	Max.		19.10	0.0015	0.0015
	Percentiles	25	1.100	0.0015	–
		75	7.900	0.0015	–
Pelagic	Numbers of data		*26*	*26*	*17*
	Mean		4.194	0.0016	–
	Median		2.250	0.0015	0.0020
	S.D.		5.776	0.0012	–
	Min.		0.033	0.0001	0.0010
	Max.		24.00	0.0047	0.0020
	Percentiles	25	0.844	0.0010	–
		75	4.900	0.0020	–
Molluscs	Numbers of data		*12*	*12*	*11*
	Mean		2.042	0.0463	–
	Median		2.000	0.0100	0.0100
	S.D.		0.745	0.0870	–
	Min.		0.222	0.0053	0.0060
	Max.		3.300	0.3100	0.3100
	Percentiles	25	1.900	0.0073	–
		75	2.400	0.0511	–

demersal fish is 0.0009 mg/kg w.w. (Table 1). The lowest In-As concentration found is below the limit of quantification (LOQ) in two species, *Dicentrarchus labrax* and *Sarpa sarpa,* fished in the same area in Sardinia (Italy) (Piras et al., 2015a,b) and a maximum of 0.260 mg/kg w.w. in *Scyliorhinus canicula* in the Adriatic Sea (Storelli et al., 2005).

Pelagic species in the Mediterranean Sea have a Tot-As median concentration of 4.60 mg/kg w.w. The minimum recorded concentration is 0.188 mg/kg w.w., found in *Engraulidae sp.* fished in Catalonia (Spain) (Olmedo et al., 2013) and a maximum of 52.41 mg/kg w.w. in *Chimaera sp.* in the Adriatic Sea (Storelli and Marcotrigiano, 2004). For In-As the median concentration reported in literature is 0.011 mg/kg w.w. The lowest In-As concentration found is 0.002 mg/kg w.w. in *Engraulis encrasicolus* fished in Thracian Sea (Kalantzi et al., 2017) and the maximum value is 0.039 mg/kg w.w. in *Sardina pilchardus* (Perelló et al., 2014).

Always in the Mediterranean Sea, molluscs show a Tot-As median value of 2.85 mg/kg w.w. The minimum Tot-As concentration is 0.172 mg/kg w.w. found in *Sepiida sp.* in Andalusia (Spain) (Olmedo et al., 2013) and a maximum of 19.06 mg/kg w.w. in *Phyllonotus trunculus* in Sardinia (Italy) (Piras et al., 2015a,b). Molluscs In-As median concentration reported in literature is 0.050 mg/kg w.w. The lowest In-As concentration is 0.001 mg/kg w.w. in *Loligo vulgaris* and *Sepia officinalis* caught in Catalonia (Spain) (Perelló et al., 2014) and the maximum concentration is 0.990 mg/kg w.w. in *Mytilus galloprovincialis* fished in Venice bay (Italy) (Argese et al., 2005).

Applying the percentages of the In-As fraction given from the literature for each subgroup to the research article where speciation was missing, we recalculated the descriptive statistics of all papers (Table 1). In the Mediterranean Sea there is not difference with the results in which In-As speciation has been conducted. For the pelagic subgroup species, we have calculated a maximum concentration of In-As of 0.216 mg/kg w.w. found in *Chimaera sp.* caught off the Adriatic sea (Storelli and Marcotrigiano, 2004) and a minimum concentration of 0.0008 mg/kg w.w. found in *Engraulidae sp.* and *Scombride sp.* fished in Catalonia and the Mediterranean coasts of Andalusia (Spain) (Olmedo et al., 2013). The maximum value is one order of magnitude higher than the results previously commented, while the minimum value is 10 folds lower than the discussed results for the same species in the same area. Molluscs in the Mediterranean Sea show the same results after the assessment of the In-As fraction, with the only exception for the minimum whose results being 2 folds lower than the results discussed above, with an In-As concentration of 0.001 mg/kg w.w. in *Sepia sp.* and *Loligo vulgaris* in Catalonia (Spain) (Falcó et al., 2006).

3.3. European Atlantic coasts

Statistical analysis did not highlight significant differences between Tot-As concentrations in seafood subgroups in European coast of the Atlantic Ocean. Tot-As concentrations bioaccumulated in seafood showed the following trend: demersal > pelagic > molluscs (Table 2). In-As concentrations showed the following trend: molluscs > pelagic > demersal (Table 2) with significant differences between subgroups ($p < 0.001$). The post-hoc Tukey test revealed significant higher concentrations in molluscs (0.0463 mg/kg w.w.) versus pelagic (0.0016 mg/kg w.w.) and demersal fish (0.0013 mg/kg w.w.) $p < 0.01$), but there are not any other significant differences among subgroups.

In this area, demersal species show a Tot-As median concentration of 2.55 mg/kg w.w. The minimum concentration is 0.066 mg/kg w.w. in *Serranus cabrilla* caught in Andalucian Atlantic Coast (Spain) (Olmedo et al., 2013) and a maximum of 19.1 mg/kg w.w. found in *Brosme brosme* in Norwegian Sea (Julshamn et al., 2012). In-As median concentration for demersal fish is 0.001 mg/kg w.w., coincident to the maximum reported value, equal to 0.001 mg/kg w.w. always in *Brosme brosme* caught in the Norwegian Sea (Julshamn et al., 2012), while the lowest In-As concentration is found in *Lepidorhombus whiffiagonis* fished in the Atlantic Coast of Andalucía (Spain) (Olmedo et al., 2013).

Pelagic species median concentration of Tot-As is 2.25 mg/kg w.w. The lowest concentration is 0.033 mg/kg w.w. found in *Thunnus thynnus* caught in the Canary Island (Spain) (Olmedo et al., 2013) and the maximum is 24.0 mg/kg w.w. found in Norwegian Sea in *Gadus morhula* (Julshamn et al., 2012). In-As median and maximum concentration on Pelagic fish is 0.002 mg/kg w.w. in *Scomber scombrus* caught in Norwegian Sea (Julshamn et al., 2012), while the lowest concentration is 0.001 mg/kg w.w. found in *Clupea harengus* and *Scomber scombrus* in Norwegian Sea (Julshamn et al., 2012).

Molluscs Tot-As median result is 2.00 mg/kg w.w. The lowest Tot-As concentration found is 0.222 mg/kg w.w. in *Mytilus sp.* caught in Galicia (Spain) (Olmedo et al., 2013) and the maximum of 3.30 mg/kg w.w. in *Mytilus edulis* fished in Hordaland (Norway) (Sloth and Julshamn, 2008). In-As median concentration in molluscs is 0.01 mg/kg w.w. The lowest concentration is 0.006 mg/kg w.w. in *Mytilus edulis* in Ostfold (Norway), while the maximum is 0.31 mg/kg w.w. always in *Mytilus edulis* caught in Hordaland (Norway) (Sloth and Julshamn, 2008).

Applying the percentages of the In-As fraction given from the literature for each subgroup to the research article where speciation was missing, we recalculated the descriptive statistics of all the paper reviewed, and no differences were observed in maximum and minimum concentrations for the demersal subgroup (Table 2). At the contrary, we see a difference in the pelagic subgroup, where the maximum concentration become 0.005 mg/kg w.w. – twice as high as the previously calculated results – found in *Trachurus trachurus* off the Portugal shores of the Atlantic Ocean (Viera et al., 2011), while the minimum is 10 times lower than the previously commented results, with a concentration of 0.0001 mg/kg w.w. in *Thunnus sp.*, fished off the Canary Island (Spain), and *Oncorhynchus sp.* (Olmedo et al., 2013). For the molluscs, after the recalculation, we have not record any variation, except for the minimum value that goes from 0.006 to 0.005 mg/kg w.w., found in *Mytilus sp.* off the shore of Galicia (Spain) (Olmedo et al., 2013).

3.4. Comparison between Mediterranean Sea and European Atlantic coasts

Overall, the greater availability in Tot-As concentration in the pelagic compartment found in the Mediterranean Sea is not present along the European coasts of Atlantic Ocean. In-As concentration shows the same bioaccumulation trend in seafood groups between the two coastal macro-areas, with significant higher concentrations in molluscs.

A comparison between Tot-As and In-As concentrations between the two areas was conducted applying the Test-t for independent samples (Fig. 1).

We did not observe any differences in Tot-As and In-As between demersal fish of the areas ($p = 0.916$ and $p = 0.124$ respectively). Conversely, pelagic fish and molluscs of the Mediterranean Sea have significantly higher concentration of both Tot-As and In-As than specimens sampled along European Atlantic coasts ($p < 0.001$).

The reasons for this wide variability in tissue concentrations of As in marine species are not fully understood, but it may be related to variations in the bioavailability of As due to environmental factors like temperature, salinity, phosphate, seasonal variations in ratios of arsenite, arsenate and Org-As in seawater, due to differences in trophic status, and due to differences in natural and anthropogenic sources. Generally, the highest Tot-As concentration are found in tissues of species that usually feed on phytoplankton or macroalgae, which often contain the highest concentration of both In-As and Org-As (Neff, 1997).

Surely, the isolation of the Mediterranean basin favours the persistence of environmental contaminants deriving from agricultural, urban and industrial waste. Furthermore, submarine volcanic emissions, or volcanic aerosol depositions, vary considerably over time and they are a strong natural component of trace elements emission in the Mediterranean Sea. Among trace element, As is known to have high concentrations in areas with volcanic geological substrate (Bubach et al., 2014, 2012; Juncos et al., 2016; Lotter et al., 2014; Zkeri et al., 2017).

Based on data reported on the reviewed literature, In-As concentrations detected in seafood are significantly lower than the available law limits, set for other foodstuffs (EFSA, 2014b).

3.5. In-As exposure risk assessment

People living in different geographical areas have different dietary patterns, particularly with regard to seafood consumption (FAOSTAT, 2017). FAO statistics report worldwide seafood per capita consumption in 2013 (g/capita/day) (Table 3) and, among some representative countries of the European coasts and northern African region, the highest total seafood consumption (demersal fish + pelagic fish + molluscs) is reported for Portugal (123 g), Norway (91 g), Spain (85 g) and France (68 g). Intermediate seafood consumers (44–49 g) are populations of Italy, Ireland, Denmark and Netherland followed by UK, Israel, Greece, Tunisia, Egypt and Germany (19–37 g). The minor seafood consumers are populations of Turkey (11 g) and Algeria (8 g). According to FAO statistics, there is also a great variability of consumption based on the specific seafood group. Usually, demersal fish are the most consumed in the aforementioned countries, followed by pelagic and molluscs (Table 3), with the exception Croatian, Danish, Israeli and Tunisian populations, who consume more pelagic fish than demersal (FAOSTAT, 2017).

This diversity in seafood consumption gives rise to different metal intake levels, which not only vary on the base of contaminant concentration in edible tissue, but also on the basis of the average daily ingestion rate (or consumption frequency) and, on the consumer body weight; therefore, health risks may differ considerably for different populations regardless of the metal concentrations found. Although the outcomes of more recent monitoring studies have been different in that they stressed that the maximum levels set by regulations of the respective countries had been frequently exceeded, a fish that exceeds the maximum food standard is not necessarily unfit for human consumption: these limits are conservatively set for regulatory purpose and assume a worst-case scenario. Moreover, there has not been any evidence of poisoning effects due to the intake of metals from the consumption of seafood in the general population (except for particular cases of pollution that occurred in the course of history, such as the methylmercury poisoning of the local population of Minamata, caused by the release of this toxic compound from an industrial wastewater of a chemical factory from 1932 to 1968). However, health risks that may stem from consumption of contaminated fish/shellfish or ingestion of contaminated water are, worldwide, of important public health concern and, it must be better understood (Ferrante et al., 2018).

To check the quality of public food supplies and evaluate consumption limits of fresh seafood, we firstly applied the equation provided by the Environmental Protection Agency for the calculation of the estimated daily intake to In-As specific for each general population of the considered countries (Table 3). Based on In-As concentrations reviewed, we found all EDI values below the BMDL0.5 suggested by WHO (3 μg/kg bw per day). Populations consuming fresh seafood caught along European coasts of Atlantic Ocean, including high frequency seafood consumers such as Norway and Portugal ones revealed the lower daily exposure to In-As and it derived mainly from the consumption of molluscs (EDI from 0.08 to 12.9 ng/kg/bw per day). French, Spanish and Portuguese molluscs' consumers have the higher EDI for this macro-area (11.6, 12.9 and 7.65 ng/kg/bw per day respectively); nevertheless, the highest values are between 233 and 392 folds below the BMDL50. Overall, the EDI derived from consumption of seafood caught along European coasts of Atlantic Ocean, with the exception of Spanish, French and Portuguese populations, is between 0.08 and 6.82 ng/kg/bw per day. By excluding mollusc subgroup, the EDI range from 0.08 to 1.65 ng/kg/bw per day.

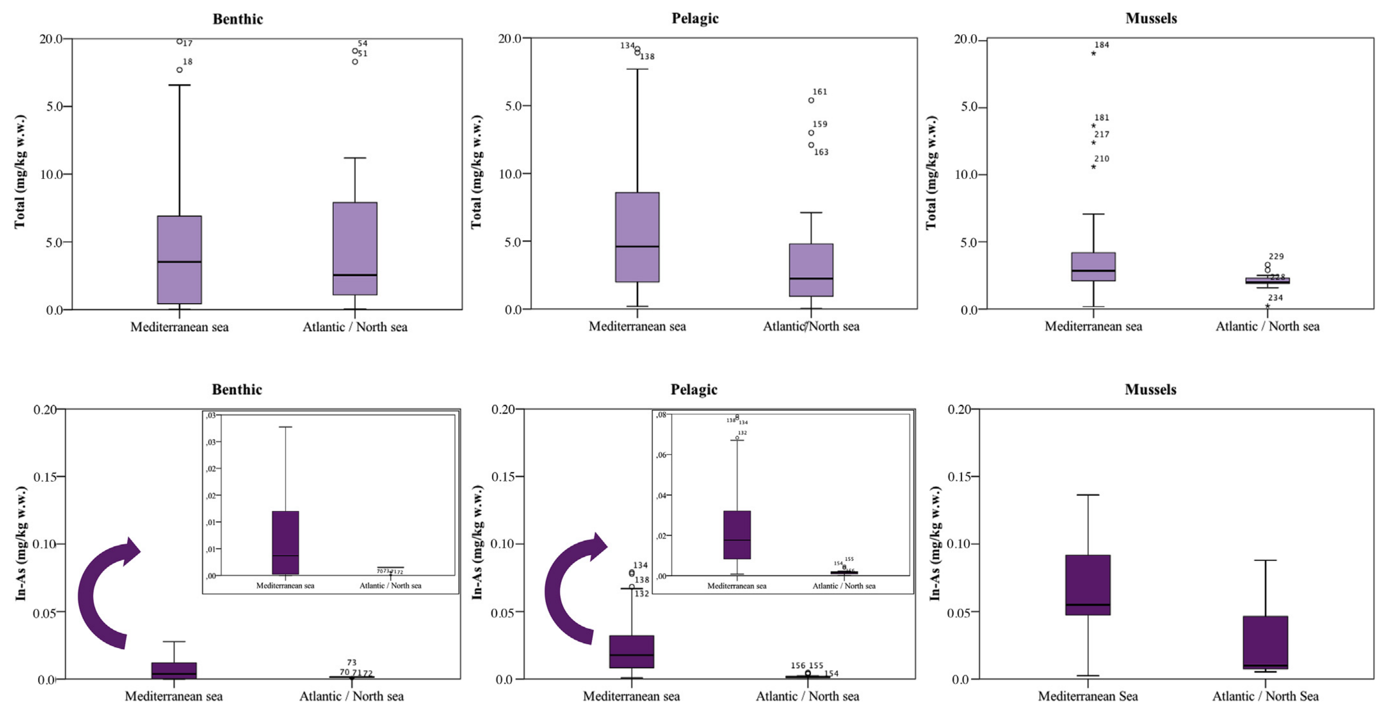

Fig. 1. Box-plot of Tot-As and In-As concentrations in seafood from Mediterranean Sea and European Atlantic coasts.

Conversely, European populations consuming fresh seafood caught along the Mediterranean Sea are greater exposed to In-As from all seafood subgroups, although EDI values are always more than 100 folds below the BMDL0.5 (Table 3). The range of the EDI derived from demersal fish consumption is between 0.51 and 6.71, from pelagic fish is between 2.85 and 10.22 and from molluscs consumption is between 1.41 and 27.17 ng/kg/bw per day respectively. Northern African countries are more exposed to In-As only from pelagic fish consumption (EDI: 2.51–8.06 ng/kg/bw per day), given the low consumption rates of the others seafood subgroups.

Overall, European populations consuming fresh seafood caught from Atlantic Ocean could have a total EDI from 0.001 to 0.013 μg/kg/bw per day and populations consuming fresh seafood from Mediterranean Sea could have a total EDI from 0.003 to 0.044 μg/kg/bw per day, with the Spanish, France and Italian populations being most vulnerable to health risks derived from oral exposure to In-As.

EFSA reports on total dietary exposure to In-As in the European population using the lower-bound (LB) and upper-bound (UB) approach. They concluded that in the adult age class mean dietary exposure to In-As ranged from 0.11 to 0.17 μg/kg b.w. per day (min LB-max LB) and from 0.24 to 0.38 μg/kg b.w. per day (min UB- max UB). The 95th percentile dietary exposure estimates ranged from 0.18 to 0.32 μg/kg b.w. per day (min LB- max LB) and from 0.44 to 0.64 μg/kg b.w. per day (min UB- max UB). If we relate our findings with the survey conducted by EFSA on total dietary exposure to In-As, we can suppose that the contribution of seafood consumption for the European populations of the Atlantic Ocean ranges from 0.6 to 2.0%, while the contribution of seafood consumption for the European populations of the Mediterranean Sea ranges from 1.6 to 6.9% of the estimated 95th percentile dietary exposure estimates (min LB - max UB). Our findings are consistent with data elaborated by EFSA for adult age class, highlighting for example an average contribution of In-As from seafood of 5% in Italy and between 8 and 10% in Spain, without distinguishing catching area of the fresh and frozen products, and including in the seafood group also amphibians, reptiles and insects. As reported by EFSA, In-As is predominant in meat, cereal, dairy and poultry, inversely Org-As compounds are more presents in seafood (EFSA, 2009).

Thus, at the light of these information, which could be the adequate consumption limits to avoid human risks due the lifetime oral exposure to In-As derived from consumption of fresh seafood? As suggested by EPA, the maximum In-As oral RfD which not to be exceeded daily, in order to not incur in chronic systemic effects such as hyperpigmentation, keratosis and possible vascular complications, is equal to 0.3 μg/kg per day. Instead, the maximum In-As oral CSF which not to be exceeded daily, in order to not incur carcinogenic effects, is equal to 1.5 mg/kg per day.

Chronic systemic effects that could arise from In-As oral exposure are several; it can affect the skin, causing the progressive decrease in blood flow, leading to gangrene and necrosis. Neurological, cardiovascular, gastrointestinal and haematological disorders are possible effects of chronic exposure (Manahan, 2002). It could induce immunosuppression of the cellular and humoral immune response in mice and chicks (Aggarwal et al., 2008; Arkusz et al., 2005), amplifying pathogen load in zebra fish (Nayak et al., 2007), altering disease risk in response to respiratory viral infection (Kozul et al., 2009). It has been shown to be embryotoxic and teratogenic in experimental animals (Golub et al., 1998; Lantz et al., 2009; Wang et al., 2006) and exposure soon after birth causes neurotoxicity resulting in behavioural changes (Rodríguez et al., 2003; Wang et al., 2006); but, there are few studies investigating such effects in human population and there are not convincing data yet (Brender et al., 2006; Shalat et al., 1996). Sex-dependent alterations in dopaminergic markers, spontaneous locomotor activity and down regulation of the antioxidant capacity of the brain was also observed (Bardullas et al., 2009). A number of studies on rats and mice have reported no symptoms of overt systemic toxicity from In-As, but observed more subtle neuro-behavioural effects (Rodríguez et al., 2003).

Our findings revealed THQ values above the level of risk (equal to 1, unitless) for high frequency consumers of molluscs (7 meals per week) among adults and children (THQ: 1.056 and 2.320 respectively) from the Mediterranean area, and for medium-frequency consumers (4 meals per week) among children (THQ: 1.332) of the Mediterranean area. Based on In-As concentrations reviewed along European coasts, only children with a high frequency consumption of molluscs have a THQ above the level of risk (1.1) (Table 4).

According to IARC monograph, there are sufficient evidence of In-As

Table 3
In-As daily intake for the general populations of representative countries of the European Atlantic coasts and Mediterranean coasts. IR: average daily ingestion rate (kg/pro capita/day); EDI: estimated daily intake (ng/kg/bw per day).

	European Atlantic coasts	IR	EDI		Mediterranean coasts	IR	EDI
Norway	Demersal	0.075	1.34	Spain	Demersal	0.037	6.70
	Pelagic	0.013	0.31		Pelagic	0.029	10.22
	Molluscs	0.003	1.82		Molluscs	0.019	27.17
	Tot. Seafood EDI		3.47		Tot. Seafood EDI		44.09
Denimark	Demersal	0.014	0.25	France	Demersal	0.032	5.70
	Pelagic	0.029	0.68		Pelagic	0.019	6.77
	Molluscs	0.004	2.32		Molluscs	0.018	24.60
	Tot. Seafood EDI		3.25		Tot. Seafood EDI		37.06
Germany	Demersal	0.011	0.20	Italy	Demersal	0.019	3.45
	Pelagic	0.007	0.16		Pelagic	0.012	4.36
	Molluscs	0.001	0.63		Molluscs	0.012	17.23
	Tot. Seafood EDI		0.99		Tot. Seafood EDI		25.04
Netherland	Demersal	0.027	0.49	Croatia	Demersal	0.010	1.82
	Pelagic	0.016	0.38		Pelagic	0.026	9.31
	Molluscs	0.002	1.39		Molluscs	0.002	2.90
	Tot. Seafood EDI		2.25		Tot. Seafood EDI		14.03
Belgium	Demersal	0.020	0.36	Greece	Demersal	0.024	4.32
	Pelagic	0.012	0.28		Pelagic	0.009	3.13
	Molluscs	0.010	6.82		Molluscs	0.003	3.60
	Tot. Seafood EDI		7.46		Tot. Seafood EDI		11.06
UK	Demersal	0.024	0.44	Turkey	Demersal	0.003	0.51
	Pelagic	0.004	0.08		Pelagic	0.008	2.85
	Molluscs	0.009	6.22		Molluscs	0.001	1.41
	Tot. Seafood EDI		6.74		Tot. Seafood EDI		4.77
Irland	Demersal	0.028	0.51	Israel	Demersal	0.015	2.68
	Pelagic	0.016	0.38		Pelagic	0.021	7.58
	Molluscs	0.004	2.83		Molluscs	0.001	0.95
	Tot. Seafood EDI		3.72		Tot. Seafood EDI		11.21
France	Demersal	0.032	0.57	Egypt	Demersal	0.010	1.79
	Pelagic	0.019	0.44		Pelagic	0.010	3.52
	Molluscs	0.018	11.64		Molluscs	0.000	0.28
	Tot. Seafood EDI		12.66		Tot. Seafood EDI		5.58
Spain	Demersal	0.037	0.67	Tunisia	Demersal	0.010	1.80
	Pelagic	0.029	0.67		Pelagic	0.023	8.06
	Molluscs	0.019	12.86		Molluscs	0.000	0.29
	Tot. Seafood EDI		14.20		Tot. Seafood EDI		10.15
Portugal	Demersal	0.092	1.65	Algeria	Demersal	0.001	0.21
	Pelagic	0.020	0.46		Pelagic	0.007	2.51
	Molluscs	0.012	7.65		Molluscs	0.000	0.03
	Tot. Seafood EDI		9.76		Tot. Seafood EDI		2.74

carcinogenicity on humans from different exposure to In-As compounds, causing lungs, skin and urinary and bladder cancer (Straif et al., 2009), and the carcinogenicity is cell-type specific (Guo et al., 1997; Kuo et al., 2017). Among the cancers found to be associated with As ingestion, bladder cancer has the highest relative risk (RR) (Chen and Wang, 1990; Guo and Lu, 1994; Wu et al., 1989). At the contrary there is no evidence of risk of cancer related to Org-As, nominally MMA and DMA (IARC, 2012; Straif et al., 2009). Results obtained from the evaluation of the cancer risk are of greater health concern, especially for the Mediterranean area (Table 4). Here, most of the values obtained are around the value of acceptable risk (ARL: 1×10^{-5}) both for high (7 meals per week) and low (1 meal per week) frequency consumers of each seafood subgroup. The CR is in the order of 1×10^{-4} for high frequency adult's consumers of pelagic fish, and for high and medium (4 meals per week) frequency adult's consumers of demersal fish and molluscs. For children of 6 years old, the risk is often in the order of 1×10^{-4} and even in the order of 1×10^{-3} for high frequency molluscs' consumers. Populations consuming fresh seafood sampled along European coasts of Atlantic Ocean have a CR significantly lower than populations of the Mediterranean area. The level of risk could be of health concern for high and medium frequency consumers of molluscs, in the order of 1×10^{-4}, both for adults and children.

4. Conclusion

Overall, the review highlighted the greater availability of In-As in the Mediterranean Sea. Seafood is an important source essential nutrients, but it is important to know how to choose species with potentially low levels of environmental contaminants. Surely, frequency of consumption of molluscs in both area should remain low to minimize In-As exposure through contaminated seafood, as well as occurrence of other contaminants, especially among Mediterranean populations. The European populations resulted more exposed to In-As are the French, Spanish, Italian and Greek ones, particularly medium and high consumers among children of 3–6 years old. Consistently to recent European Food Safety Authority (EFSA), World Health Organization (WHO) and Food and Agriculture Organization (FAO) recommendations, seafood should be consumed with a frequency of 1–2 servings per

Table 4
Target hazard quotient and cancer risk estimate for inorganic As at different levels of exposure. THQ > 1 and CR > 10^{-5} are reported in italic.

Mediterranean Sea	Level of exposure (days per week)	THQ - Adult	THQ - Child	CR - Adult	CR - Child
Benthic Fish	7	0.135	0.297	6.08E-05	*1.34E-04*
	4	0.077	0.169	3.46E-05	7.61E-05
	1	0.019	0.042	8.66E-06	1.90E-05
Pelagic Fish	7	0.271	0.596	*1.22E-04*	*2.68E-04*
	4	0.155	0.340	6.96E-05	*1.53E-04*
	1	0.039	0.085	1.74E-05	3.82E-05
Molluscs	7	*1.056*	*2.320*	*4.75E-04*	*1.04E-03*
	4	0.602	*1.322*	*2.71E-04*	*5.95E-04*
	1	0.150	0.331	6.77E-05	*1.49E-04*
European Atlantic coasts	Level of exposure (days per week)	THQ - Adult	THQ - Child	CR - Adult	CR - Child
Benthic Fish	7	0.014	0.031	6.32E-06	1.39E-05
	4	0.008	0.018	3.60E-06	7.92E-06
	1	0.002	0.004	9.01E-07	1.98E-06
Pelagic Fish	7	0.017	0.038	7.78E-06	1.71E-05
	4	0.010	0.022	4.44E-06	9.74E-06
	1	0.002	0.005	1.11E-06	2.44E-06
Molluscs	7	0.500	*1.100*	*2.25E-04*	*4.95E-04*
	4	0.285	0.627	*1.28E-04*	*2.82E-04*
	1	0.071	0.157	3.21E-05	7.05E-05

week (EFSA, 2014b; FAO/WHO, 2010).

From this review arise the growing need to better characterize the In-As in fresh, processed and cooked seafood, given the limited data available from the literature, as well as the exposure risk from the total diet, that will be exploited to generate reliable occurrence data that can be used to correctly evaluate the need for setting additional maximum levels and consumption limits for other food commodities.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.01.010.

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