A global retrospective study on human cases of tetrodotoxin (TTX) poisoning after seafood consumption

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Title:

A global retrospective study on ~~H~~human cases of tetrodotoxin (TTX) poisoning ~~intoxication due to the ingestion of~~after seafood ~~products containing tetrodotoxin: a global retrospective study~~ consumption

Running head:

Human cases of TTX poisoning worldwide

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Abstract

The present~~A~~ global retrospective study on human cases of tetrodotoxin (TTX) intoxication caused by seafood consumption was ~~conducted~~aimed at updating the relative risk according to seafood product categories and geographical areas. Overall, 3032 cases from five continents were collected, mainly from Asia. Over~~More than~~ half of them~~ cases~~ were attributed to fish, followed by gastropods, arthropods and cephalopods. ~~The intoxication source and its origin varied between geographical regions: i~~In South East and East Asia intoxications derived from all the aforesaid seafood product categories, locally sourced; in Oceania, Sub-Saharan Africa and Centre-South America from local pufferfish. In Europe dated cases were caused by imported Asian products, as in North America. However, recent intoxications in Spain and in Middle East and North Africa, caused by locally caught products, confirm the occurrence of TTX even in areas previously ~~marginally~~ not affected by this public health issue.

Keywords:

Pufferfish, marine toxins~~, human poisoning, toxic fish species~~, public health, tetrodotoxin, risk

1. Introduction

Tetrodotoxin (TTX) is one of the most potent neurotoxins known [1] and the most commonly involved in lethal marine poisoning [2]. In fact, TTX intoxication can be defined as a paralytic syndrome and it is part, together with ciguatera poisoning and Paralytic Shellfish Poisoning (PSP), of a group of major marine intoxications with neurological involvement [2]. TTX ~~is a water-soluble heterocyclic guanidine that~~ blocks Na+ conductance ~~(Isbister and Kiernan 2005)~~, inhibiting ~~the~~its passage ~~of this ion~~ into the membranes of excitable cells, such as muscle and nerve tissue, leading to immobilization [3]. Clinical signs develop rapidly, usually between 10 minutes and 15 hours after ingestion of contaminated seafood products [4-6]. Early neurological symptoms include perioral and distal limb numbness and may be associated to nausea and vomiting. Severe poisoning causes generalized flaccid paralysis and cardiovascular effects. The severity of symptoms is dose-dependent, and death mainly occurs due to respiratory failure [1-2]. Since no specific antidote is available, therapy is mainly represented by aggressive supportive and symptomatic treatment [7].

~~Tetrodotoxin (TTX) is one of the most potent neurotoxins known (Hwang and Noguchi 2007) and the most commonly involved in lethal marine poisoning (Isbister and Kiernan 2005).~~ The name TTX derives ~~in fact~~ from the Teleost fish order Tetrodontiformes ~~(Nagashima & Arakawa 2016Hanifin 2010)~~, as the toxin has been isolated from members of this taxa, in particular from Tetraodontidae (pufferfish) [8-9]. In Japan pufferfish are considered a delicacy and TTX intoxication is an historically known issue [10]. ~~In the past TTX was believed to be exclusively present in this taxonomic group (Noguchi and Arakawa 2008).~~ However, TTX has been ~~subsequently~~ isolated also from~~in~~ other marine organisms such as tropical fish ~~of the~~ of the Gobiidae family ~~in Asian~~ [11], marine gastropods [12-15], bivalves [16-19], cephalopods (only

Hapalochlaena spp., family: Octopodidae) [20], arthropods (only *Carcinoscorpius rotundicauda* and crabs of the Xanthidae family) [1, 21], as well as Echinodermata (starfish, Astropectinidae), several taxa of worms (Turbellaria, Nemertinea, Anellida Polychaeta, Chaetognata) and algae [9]. Besides this wide range of marine species, TTX has also been isolated from a single class of terrestrial vertebrates (Amphibia: frogs and newts) [22]. Subsequently, an exogenous origin of TTX [9, 23] with marine bacteria as a primary source [17] has been hypothesized. ~~Further discovers, such as TTX production by marine bacteria and the absence of TTX toxicity in farmed pufferfish fed with non-toxic diets, together with the widespread occurrence of TTX in numerous phylogenetically unrelated taxa, allowed hypothesizing an exogenous origin (Magarlamov, Melnikova, and Chernyshev 2017; Noguchi and Arakawa 2008) with marine bacteria as a primary source (EFSA CONTAM Panel 2017).~~ According to a recent literature review, 31 different bacteria genera able to produce TTX have been isolated until 2017, among which the most common is *Vibrio* spp. [23]. However, the pathway of TTX bioaccumulation in marine ecosystems is still subject to debate [23-24].

~~TTX intoxication can be defined as a paralytic syndrome and it is part, together with ciguatera poisoning and Paralytic Shellfish Poisoning (PSP), of a group of major marine intoxications with neurological involvement (Isbister and Kiernan 2005). TTX is a water-soluble heterocyclic guanidine that blocks Na+ conductance (Isbister and Kiernan 2005), inhibiting the passage of this ion into the membranes of excitable cells, such as muscle and nerve tissue, leading to immobilization (Denac, Mevissen, and Scholtysik 2000). Clinical signs develop rapidly, usually between 10 minutes and 15 hours after ingestion (Arakawa et al. 2010; Chew et al. 1983; Chowdhury et al. 2007). Early neurological symptoms include perioral and distal limb numbness and may be~~

~~associated to nausea and vomiting. Severe poisoning causes generalized flaccid paralysis and cardiovascular effects. The severity of symptoms is dose-dependent, and death mainly occurs due to respiratory failure (Hwang and Noguchi 2007; Isbister & Kiernan 2005). Since no specific antidote is available, therapy is mainly represented by aggressive supportive and symptomatic treatment (Salzman, Madsen and Greenberg 2006).~~

Considering the high severity of TTX poisoning and since intoxication following consumption of pufferfish is well known worldwide, many governments have banned or restricted their consumption and trade. In Asia, where the problem is historically known and TTX intoxication is one of the most frequent fish poisonings [25], many countries developed specific legislation. Japan is the country in which legislation is more articulate and establishes, since 1958, that the chefs must have a license to cook dishes based on puffer fish. Moreover, an official list concerning edibility of various species of pufferfish and their tissues exists since 1983 [9] and is regularly updated [26]. Beside this country, restrictions are in place in China [27], Thailand [28], Taiwan [29], Vietnam [30], in the USA [31] and in Europe [32]. ~~2011), Taiwan (Huang et al. 2014) and Vietnam (Cong and Tuan have banned or restricted the use of pufferfish. Limitation are in place also in the USA, where a single company is allowed to import *Takifugu rubripes* for restaurants. Moreover, consumption of local pufferfishes caught in coastal waters of the mid-Atlantic (between New York and Virginia state) is admitted since these are considered free from the toxin, while the State of Florida currently has a ban on both commercial and recreational harvesting of pufferfish (https://www.fda.gov/food/recallsoutbreaksemergencies/safetyalertsadvisories/ucm085458.htm; https://www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding/u~~

em107601.htm)~~. Europe has a very stringent legislation as regards poisonous fish and marine biotoxins. In fact, according to the Reg. (CE) n. 853/2004 "*Fishery products obtained from poisonous fish of the following families must not be placed on the market: Tetraodontidae, Molidae, Diodontidae and Canthigasteridae*".~~

~~Tt~~The very wide range of organisms that can host TTX, the complexity of the global seafood market, together with human intervention on the environment and climate change, has enhanced the risk of consumption of TTX-contaminated food also in countries not historically affected by this issue. Increasing worldwide trade of seafood products favors TTX intoxication due to fraudulent episodes [28, 33] or to illegal importation [34-35]. ~~The arrival in 2003 of the toxic pufferfish *Lagocephalus sceleratus* from the Red sea (Akyol et al. 2005), favored by~~

~~A~~A~~a~~nthropogenic environmental modification and climate change have introduced TTX as an emerging public health problem in the Mediterranean area [36-37]~~ due to the arrival in 2003 of the toxic pufferfish *Lagocephalus sceleratus* from the Red sea (Akyol et al. 2005)~~. At least eleven species of the family Tetraodontidae have been reported in the Mediterranean Sea [38]. The arrival in 2003 of the toxic Lessepsian species *L. sceleratus* from the Red Sea aroused strong interest as it represents a potential public health hazard. In fact, several studies have confirmed the presence of TTX in this species [36, 39-42]. In addition, the toxin was also found in *Lagocephalus~~.~~ lagocephalus* [43] and recently in *Torquigener flavimaculosus* [44] and *L. suezensis* [42]. Similar factors are believed to be responsible of the spreading of TTX along the North East Atlantic Ocean coasts [45~~M. J. Silva et al. 2012~~].

The aim of the present work was to conduct a global retrospective study on human cases of intoxication due to the ingestion of seafood products containing TTX, considering that ~~a~~ single outbreaks are often described in case reports and a similar comprehensive review on this topic is lacking. Therefore, ~~. In fact,Although other available reviews on TTX intoxication exist (EFSA CONTAM Panel 2017; Hwang and Noguchi 2007; Lago et al. 2015; Noguchi and Arakawa 2008; Panao et al. 2016)~~ ~~, they deal with general characteristics of the toxin and only report some intoxications cases from different geographical area. Besides, many single outbreaks are described in case reports~~ and~~. Since all these fragmentary data are fragmentary and had not been systematically reviewed altogether.~~ ~~, the aim of the present work was to conduct a global retrospective study on human cases of intoxication due to the ingestion of seafood products containing TTX. Specific attention was paid to the geographical area of the intoxication, the source and its origin (local or imported)~~. ~~in order to better characterize the risk factors mainly involved in human intoxication. from~~ by gathering fragmentary data on TTX intoxication, outcomes from the present study could be useful to fulfil the actual knowledge gap on the relative risk related to different food products and geographical areas associated to this hazard~~, in order~~. This is particularly relevant in the light of complex anthropogenic and environmental factors, including climate change, that could modify the patterns of human intoxication. ~~In fact, the complex anthropogenic and environmental scenario influences possible patterns of intoxication.~~

2. Materials and methods

2.1. Literature search and selection of cases

To review global cases of TTX intoxication in humans, literature data was searched on PubMed and Google Scholar databases using the following keywords: (Tetrodotoxin OR TTX) AND (Poisoning) AND (Human OR Human case) AND (Europe OR America OR United States OR USA OR Africa OR Oceania OR Australia OR Asia). The search was conducted using the terms altogether or differently combined in order to retrieve the maximum number of records. Cases described in Japan were excluded from the analysis, since the traditional consumption of pufferfish in this country makes the cases of intoxication very common and consequently not always reported in scientific articles in English. Thus, a literature search could be biased and give incomplete information on the real incidence of cases in this country. Furthermore, data on the incidence and prevalence of TTX intoxications in Japan are already available [1, 4, 9, 46]. An updated list of cases occurred between 2003 and 2017 is also reported ~~,~~on the website of the Ministry of Health, Labour and Welfare of Japan [47]. The reference list of the screened articles was also checked for eligible new records and Google Scholar search option "cited by" was also used. Papers published in English, French, Italian, Spanish and Portuguese were included. Articles in other languages were also used if they presented an English abstract with sufficient details (see below). The search was concluded in April 2018. After deduplication, cases were considered eligible and included in the study when the following information was provided: i) number of intoxicated people; ii) geographical location/place of intoxication (at least at country level); iii) source of intoxication (at least the category of seafood responsible of intoxication). Cases included in the study were supported by clinical (including anamnesis and typical symptoms) and/or laboratory diagnosis.

2.2. Data Extraction

For each study, besides the minimal information (number of intoxicated people; geographical location/place of intoxication; source of intoxication) the following additional data were extracted, when available: date of intoxication, number of fatalities, age, sex, geographical origin of the source of intoxication and the part of the food source consumed (available only for fish products). All data were extracted using predefined fields in an Excel file. In order to process data from countries with similar geographical characteristics and bordering the same sea/ocean, the cases relating to

America were subdivided into North America and Centre/South America, while data from Asia and Africa were further subdivided and regrouped in the following sub-areas: South-east and East Asia, Middle East and North Africa and Sub-Saharan Africa. This division will be maintained in the subsequent analysis and discussion of the data. For the purposes of this work, products originating from the same geographical sub-area where the case of intoxication was reported from were considered locally sourced, as opposite, the others were defined imported.

2.3. Statistical analysis

Associations among variables were investigated using chi-square test for finding significant differences. Results were considered significant when $p<0.05$ and highly significant when $p<0.001$. Investigated couples of associated variables were: i) geographical location of the intoxication and total number of cases; ii) geographical location and number of fatal cases; iii) intoxication source and total number of cases; iv) intoxication source and number of fatal cases; v) geographical location of the intoxication and origin of the intoxication source. All statistical analyses were performed using the software SPSS ® vs 15 for windows.

3. Results

3.1. Literature search, cases of intoxication, fatality rate, age and sex distribution

Totally, 142 scientific articles were selected and analyzed. The articles included in the study mainly described single outbreaks occurred in different areas of the world. Besides, data were collected also from 7 reports or newspaper articles cited in the reference list of some articles. Out of all these records, 3032 cases matched the inclusion criteria. In the large majority of the cases, no laboratory analysis was carried out to confirm the toxin involved and the TTX intoxication was clinically diagnosed on the basis of the anamnesis and of the symptoms (n=2641, 87.1%). Only 375 cases were supported by a wide range of toxicological tests, often combined (detailed in Table 1SM). In addition, in 16 cases it was reported that the presence of TTX in the source was confirmed, but the test used was not specified.

Out of the 3032 cases, at least 341 were fatalities (11.2%). Overall, precise age was available only for 304 cases of intoxications (10.0%). In these cases, the intoxication showed the highest frequency in children under 10 (23.3%), followed by thirties (20.3%), forties (18.0%), fifties (11.5%), under 20 (11-20 years of age) (10.5%), twenties (9.5%), over sixty (6.5%). In addition, in 169 cases the mean age was reported and in 517 cases an age range was indicated. The overall range was 4-74. As regards the sex ratio, gender was available for 1335 cases (44.0%): 898 were males (67.3%) and 437 were females (32.7%).

3.2. Geographical location

Cases were reported from five continents (Fig. 1). The vast majority of the cases were described in Asia (Japan excluded, see section 2.1) (n=2686, 88.6%), followed by Africa (n= 203, 6.7%), America (n=90, 3.0%), Oceania (n=39, 1.3%) and Europe (n=14, 0.5%). As mentioned, data from America were subdivided into North America (n=23, 0.8%), Centre/South America (n=67, 2.2%), while data from Asia and Africa were further subdivided and regrouped as follows: South-East and East Asia (n=2668, 87.9%), Middle East and North Africa (n=168, 5.5%) and Sub-Saharan Africa (n=53, 1.7%). Complete details are given in Table 1. A significant difference in the fatality rate was observed in relation to the geographical area, both in terms of continents and in terms of sub-regions. As regards continents, Asia showed the lowest fatality rate (10.4%), while the other 4 continents were comparable (15.4-21.4%). As regards the sub-areas, Sub-Saharan Africa, Europe and North America showed statistically higher fatality rates (20.8-30.4%) (Table 2).

3.3. Source of intoxication

The source of intoxication was ~~represented by~~ fish in 1817 cases (59.9%), gastropods in 634 cases (20.9%), arthropods in 492 (16.2%) and cephalopods in 89 (2.9%) (Fig. 2). Data on the source of intoxication are detailed in Table 3 and briefly presented below. Among the fish category, most of the cases (n=1703, 93.7%) were due to the ingestion of fishes of the order Tetraodontiformes. Of these, 1239~~40~~ were generically indicated as pufferfish. The remaining cases were due to the ingestion of species of different Tetraodontidae genera such as *Takifugu*, *Lagocephalus*, *Arothron*, *Tetrodon*, *Sphoeroides*, or to the ingestion of *Diodon* spp. (n=10) (Diodontidae - Porcupinefish) or of species of the Ostraciidae family (n=4) (Boxfish). The other fish species belonged to the family Gobiidae (Perciformes) (n=33, 1.8%) or were not identified (n=82, 4.5%) (Table 3). As regards gastropods, the large majority of intoxications (n=618, 97.5%) were attributed to the consumption of members of the order Neogastropoda, family Nassaridae and especially to species of the genus *Nassarius* spp. (n=468). A small number of cases was attributed to *Natica fasciata*, *Charonia lampas*, *Oliva* spp., *Neverita didyma* and to not identified gastropod species. Interestingly, intoxications due to the consumption of arthropods were exclusively due to *Carcinoscorpius rotundicauda* (horseshoe crab). Similarly, only one species, *Hapalochlaena fasciata* (blue-lined octopus), was involved in the cases related to the consumption of cephalopods (n=89) (Table 3).

A significant difference in the fatality rate was observed in relation to categories of the sources involved. In fact, the fatality rate was significantly higher following the consumption of fish products (16.3%) rather than other products categories (gastropods 4.9%, arthropods 2.4% and cephalopods 2.2%).

3.3.1 Source of the intoxication in relation to the geographical sub-area

The distribution of the different categories of product implicated in cases of intoxications in relation to the sub-areas are summarized in Fig. 3 and described in detail in Table 1 and Table 2SM. Only in South East and East Asia all the categories were implicated: fish was responsible for around half of the intoxications (n=1454, 54.5%), followed by gastropods (n=633), arthropods (n=492) and cephalopods (n=89). The only other sub-area where two categories were implicated was Europe (Table 1).

As regards South East and East Asia more in details, most intoxications caused by fish were attributed to species belonging to the order Tetraodontiformes (n=1354, 93.1%). Other fish species responsible for intoxications were gobiids, which do not belong to this order and were reported as intoxication source exclusively from Asia, mainly from China (n=22) and to a lesser extent from Taiwan (n=11). Of the 633 cases attributed to gastropod consumption in Asia, the vast majority of them (n=547, 86.4%) occurred in China, followed by Taiwan (n=74, 86.4%) and Vietnam (n=547, 86.4%).

C. rotundicauda intoxications (n=492) mostly occurred in Thailand (n=457), followed by Malaysia (n=30) and China (n=5). Intoxication cases caused by the consumption of a cephalopod retrieved in this study were found in Taiwan and Vietnam (n=2 and n=87 respectively).

In Middle-East and North Africa, except for 12 cases for which the fish species was not identified, the remaining 156 cases were generically attributed to pufferfish (n=62) or specifically to *Lagocephalus sceleratus* (n=94). This species was the only responsible for intoxication in Israel (n=16) and Lebanon (n=2) and the responsible for most of the cases occurred in Egypt (n=76/147). Similarly, the limited number of TTX poisonings in Centre and South America (n=67) were generically attributed to pufferfish (n=47) or to a single pufferfish species, which in this subarea was *Sphoeroides* spp. (n=18). Also, the 53 cases reported in Sub-Saharan Africa, were exclusively caused by the consumption of pufferfish. They mainly occurred in the islands of the Western Indian Ocean, in particular on the Island of Reunion (n=33), Madagascar (n=17) and Zanzibar (n=1). As regards Oceania, TTX intoxications were mainly described in Australia (n=31, 79.5%) and exclusively caused by several species of fish belonging to the order Tetraodontiformes. In North America 23 TTX intoxications were reported, only from the United States and exclusively caused by pufferfish. The most implicated genera were *Lagocephalus*, in particular *L. lunaris* (n=4) and *Arothron* (n=4). Other identified species were *Diodon hystrix* (n=1) and *Sphoeroides testudineus* (n=1).

Finally, as regards Europe, the numerically scarce intoxications (n=14) are for the most part fairly dated and caused by pufferfish (n=13). The only remaining case occurred in October 2007 in Malaga, Spain, following the consumption of marine gastropods (*Charonia lampas lampas*) caught in the Southern coast of Portugal.

3.3.2. Anatomical part of the seafood consumed

The anatomical part consumed was indicated only for fish and in 287 cases of intoxication (16.8%). Flesh was consumed in 121 cases (42.2%), gonads in 73 cases (25.4%) and liver in 33 cases (11.5%) (Fig. 4). Different combinations of these body parts were ingested in the remaining 60 cases.

3.3.3. Geographical origin of the source of intoxication

Overall, data on the geographical origin of the food source was available for 1114 cases (36.7%). The large majority were locally sourced (n=1090, 97.8%), while the remaining cases were imported (n=24, 2.2%). Differences related to the geographical areas were observed: in South East and East Asia, all the cases with known origin derived from locally sourced seafood products. Similarly, in Middle East and North Africa, the 27 cases with known origin were all due to local specimens, originating from the Mediterranean or the Red Sea. Also, in Centre-South America, Sub-Saharan Africa and

Oceania all the cases with known origin were due to locally fished species. On the contrary, in North America all the cases with known origin were related to fish imported from Asia (China, South Korea, Japan). Finally, as regards Europe, 13 of the 14 reported cases were due to imported fish (92.9%) while one case was due to the consumption of local gastropod (Table 2SM).

4. Discussion

4.1. Cases of intoxications and diagnosis, fatality rate and toxicity of the seafood category

4.1.1. Cases of intoxications and diagnosis

The diagnosis of TTX intoxication is generally clinical [2], often supported by a medical history that indicates the previous consumption of seafood products~~. Also, the identification of the species responsible for the intoxication, for example by the alimentary remains, can decisively direct the diagnosis~~ [48-51]. The present results confirmed this trend, as in 87.1% of the cases~~,~~ no laboratory analysis was performed (or not reported)~~, neither to evaluate the toxicity of the products, nor to identify the toxin~~. Although the lack of a supporting laboratory analysis represents a limit of the present study, the exclusion of cases relying only on clinical diagnosis would strongly underestimate the global occurrence of cases. However, toxin identification might be important to differentiate TTX intoxication compared to saxitoxin (STX) intoxication, both inducing similar symptoms. Moreover, both toxins can be isolated from the same species, including pufferfish [13, 50]. T~~o this end, the use of t~~he mouse bioassay (MBA), important to quantify toxicity, if used alone as ~~it results~~ in 102 cases (3.4%) ~~included in the present work~~ (Table 1SM), is not useful to discriminate the two toxins [17]. For the identification of the specific toxin ~~it is therefore important to apply~~ chemical-analytical or serological methods for analysing the fishery product, the food residue or the patient's blood or urine should be applied [2], as occurred in 273 cases (9%)(Table 1SM).~~, for analysing the fishery product, the food residue or the patient's blood or urineThe research ofor TTX by HPLC allows its simple quantification of TTX in urine and serum. However, while TTX ins serum TTX maybe is undetectable after 12-24h, TTXit can last up to 5 days in urine up to 5 days (Isbister and Kiernan 2005; Oda et al. 1989; O'Leary, Schneider, and Isbister 2004).~~

4.1.2. Fatality rate and toxicity of the seafood category

Although the number of TTX intoxication cases in Asia is the highest, it is interesting to note that the fatality rate (10.4%) is statistically significantly lower than the other continents (Table 2). Beside the consumption of categories of products (arthropods and gastropods) associated with a low fatality rate (see section 3.3), maybe this can ~~also~~ be explained in terms of a quicker recognition of symptoms by clinicians and of a better clinical management of intoxications, acquired over time in this region, as already hypothesized by Yin et al. [51] ~~(Yin et al. 2005)~~. A similar low fatality rate (8.3%) was in fact reported for Japan [1].

The reason behind the higher fatality rate associate to fish products was investigated collecting the results of the MBA for the cases related to fish ingestion (available in 137 cases out of 1817, 7.5%) (Table 3SM). Fish eggs, and more rarely liver and skin, may overcome the toxic threshold of 1000 MU/g. Values between 100-1000 MU/g were frequently observed for the same tissues. MBA data from gastropods involved in intoxications (available in 109 cases out of 634, 17.2%) showed more frequently moderate toxicity (100-1000 MU/g). These concentrations, together with the utilization of different part of the fish as traditional food in some countries [52], might be the explanation of the statistically significant ~~differences observed for~~ higher fatality rate.

Data on MBA results were not available for *C. rotundicauda* (horseshoe crab) and *Hapalochlaena* spp. in the studies included in the analysis. However, ~~the~~ a low toxicity of the horseshoe crab was ~~evaluated in several works~~ shown~~ing low toxicity level~~ in Thailand [53], Bangladesh and Cambodia [54-55]. Toxicological ~~D~~data on ~~the toxicological profile of~~ species of *Hapalochlaena* are described in ~~scarce. I~~n a few studies showing~~y~~ the presence of the toxin in different organs ~~was shown~~ [56-58]. Recently, the evolution and origin of TTX acquisition in the blue-ringed octopus has been reviewed [59].

4.2. Geographical location, source of intoxication and its origin

4.2.1. South East and East Asia

~~*4.2.1.1. Source of intoxication.*~~ The fact that ~~M~~most cases of TTX intoxications (88.6%) occurred in Asia is not surprising and is in agreement with the literature data [1-2, 60-61]. In fact, until 2005, TTX was mainly present in the warm waters of East and Southeast Asia [10], and in particular Japan [34], Korea [62], China [63-64], Taiwan [65-66], Thailand [67] and Bangladesh [21, 68].

Fish products. The present study supports the fact that TTX intoxications caused by pufferfish are still widespread in all Asia coastal countries ~~(M. S. Islam et al. 2011)~~. In Thailand, which was found as the country with the highest number of intoxications (29.5% of the total intoxications in South-East and East Asia), pufferfish is in great demand for its cheapness and its neutral taste ~~(Chulanetra et al. 2011). Pufferfish are caught~~ and is frequently sold illegally~~, whole, in pieces and~~ in the form of fish-balls~~, mixed with meat of other species, and they are available in specific restaurants called "*Moo-Kata*", which have become popular for this product~~. Their fraudulent sale ~~of fishballs sold as salmon but containing toxic pufferfish~~ resulted in about 115 poisonings and 15 deaths in the country in 2007 [28]. In Taiwan and China~~, although~~

~~people do not consume pufferfish as frequently as in Japan and there are large restrictions in place~~, poisoning for consumption of wild specimens occurs fairly frequently~~ (Arakawa et al. 2010)~~. ~~Also i~~In Taiwan, poisoning cases are often due to substitution of edible species with puffer roe or muscle [1]. In Bangladesh, ~~while the coastal communities seem to be aware regarding the potential toxicity of pufferfish, the~~3 main outbreaks, involving 141 people in 2008, occurred in inland areas where the inhabitants, differently from coastal communities, ignored the potential toxicity of these species [69]. Poverty and food shortages~~ affecting a large part of the population of the country~~, together with a lack of control measures by the food safety authorities, increase the risk of poisoning, as pufferfish or their wastes ~~not properly disposed of, ~~are easily available in local markets at low cost [60, 69]. ~~The socio-economic context of P~~Poverty and malnutrition may also partly explain the high mortality rate in this country, around 20.2%, almost twice the Asian average (11.3%). In Vietnam, especially in rural areas, pufferfish ~~are believed to be frequent responsible for intoxication since they ~~are readily available and considered a delicacy, although their commercialization is ~~actually ~~banned [30].

The intoxications due to Gobiidae were observed only in China and Taiwan, likely due to the fact this seafood is usually consumed in Chinese coastal regions [70]. To date only 4 species of the Gobiidae family are known to be toxic due to the presence of TTX and ~~currently ~~the sale or consumption of gobiids in China is not restricted. Interestingly, several ~~intoxicated ~~patients declared that they were not aware of the toxicity of these fish and that they had consumed them previously~~, without any consequence~~ [71].

Gastropod products. Most cases occurred in Taiwan and China, countries with a long tradition of consumption of small detritivorous gastropods, considered a delicacy in fishing villages and an economic nutritive food [72]. Marine gastropods are ~~historically~~ involved in intoxications ~~(Arakawa et al. 2010; Noguchi and Arakawa 2007)~~since they can effectively concentrate TTX if present in the marine environment [10], even by the consumption of dead puffers [73]. ~~Therefore, prevention must include the prohibition of consumption of gastropods in Asian areas affected, unless coming from certified marine areas (Shui et al. 2003).~~

Arthropod products. Cases of intoxications due to its consumption were only reported from Thailand, Malaysia and China. In fact, eggs of the horseshoe crab *C. rotundicauda* are frequently used to prepare traditional Thai dishes [74]. In Malaysia, horseshoe crabs' eggs or flesh are consumed mainly in coastal regions, where the inhabitants claim to know which parts of the animal need to be discarded to avoid adverse effects [75]. In addition, the misidentification of *C. rotundicauda* with a ~~similar~~ morphologically similar edible species, *Tachypleyus gigas*, enhances the intoxication risk [1]. The incorrect local beliefs that the toxin is inactivated by cooking, or that it is possible to distinguish between toxic and non-toxic *C. rotundicauda* specimens, are additional causes. *C. rotundicauda* is also consumed in Bangladesh, but studies on specimens caught in the local Bay of Bengal have shown a very low TTX content [55] and~~. In fact,~~ no intoxications from this product were reported in this country.

Cephalopod products. Octopus of the genus *Hapalochlaena* spp. inhabit the shallow waters of Australia and Southeast Asia [20]. *Hapalochlaena* spp. octopus were found to be frequently responsible for TTX poisoning following inoculation through the bite, for example in Australia and Singapore [56, 76], while the intoxication as a result of food consumption is believed to be rare, as confirmed by the present study.

~~*4.2.1.2. Origin of the source of intoxication.*~~ All the South East and East Asian cases with known origin derived from locally sourced seafood products. Even for cases not reporting this information the origin could be considered as local based on the distribution area of the species responsible for intoxication. This is not surprising considering that in Asia the presence of TTX is an endemic problem [10]. ~~In addition, factors such as culinary traditions, poverty and weak control by the competent authorities in some countries, as well as legislative deficiencies, favour the intoxication occurrence (How et al. 2003; M. S. Islam et al. 2011; Q. T. Islam et al 2011; Lewis 2017).~~

~~For this reasonreason,,~~ Consequently, several Asian countries issued a specific legislation. In China a ban on trading and consuming products derived from pufferfish remained in force from 1990 to 2016, although breeding for export was allowed. At the end of 2016, this ban was removed and two farmed species (*Takifugu rubripes* and *Takifugu obscurus*) were reintroduced on the internal market [27~~http://www.newschinamag.com/newschina/articleDetail.do?article_id=910&section_id=26&magazine_id=~~]. Among the other Asian countries also Thailand [28], Taiwan [29] and Vietnam [30] have banned or restricted the use of pufferfish.

4.2.2. Middle East and North Africa

Intoxication in this region were frequently attributed to *L. sceleratus*. Interestingly, the intoxication cases caused by this species are quite recent (91 after 2005 and 3 in which the date is not specified but reported by recent works). These data are related to the recent invasion of the Mediterranean Sea by this species that reached the Eastern Mediterranean in 2003 [77], following a Lessepsian migration through the Suez Canal (Guardone et al. 2018). In addition to these cases, a serious case of intoxication by *L. sceleratus* was registered in August 2013 in Tunisia, in the inland town of Gafsa [78].

Since no sufficient details were available for the intoxication (number of patients involved), it was not included in the analysis. ~~This incident occurred despite a national awareness campaign following the commercialization of *L. sceleratus* in the internal areas of the country, where people, as in Bangladesh (Islam et al. 2011b), were not aware of the risks posed by this species (Ben Souissi et al. 2014).~~ Considering the high toxicity and the widespread diffusion of *L. sceleratus* in the Mediterranean Sea [38], it is reasonable to assume that ~~this species~~it may also be involved in part of the remaining 74 intoxications in this geographical area (of which at least 60 occurred after 2003), although the source was identified only as "generic pufferfish", "unidentified fish" and "Tetraodontidae".

Data arising from the analysis of the origin of the intoxication source which, when available, was always local, support the role of *L. sceleratus* as an emerging problem of food safety and public health in the Mediterranean [36-38]. ~~This issue lead in fact to various informative interventions and initiatives to prevent its consumption in the countries bordering the Mediterranean basin (Andaloro et al. 2016; Ben Souissi et al. 2014; Kalogirou 2013).~~

4.2.3. Central-South America

Although pufferfish is not a typical dish of Brazilian cuisine, and intoxications are rare [50], in some regions of the north-east of the country it is consumed routinely [79]. The involvement of the genus *Sphoeroides* is in agreement with its geographical distribution and toxicity. In fact, it is one of the most common pufferfish genus in the waters facing Brazil [80]. This widespread occurrence favours the local origin of the source of intoxication. In Brazil, in fact, the intoxication by pufferfish mainly occurred as a family event~~, often involving at the same time people from the same family or groups of fishermen who consumed the fish they caught~~ [50, 80].

~~As for Mexico, the second country in the area by number of intoxication cases,~~ ~~t~~The pufferfish species found along the Mexican coast have long been considered non-toxic and edible and ~~consequently no legislative measures have been adopted. Interestingly,~~ at the beginning of 2000s, Mexico was one of the largest exporters of pufferfish in the world, ~~with almost 200 tons caught near Baja California~~ [81]. However, TTX was found in at least one organ~~,~~ in 4 of the 5 species fished near the Mexican Peninsula of Baja California (*Sphoeroides annulatus, Sphoeroides lobatus, Arothron meleagris* and *Canthigaster punctatissima*) [82] where poisonings were reported between 1970 and 1995 [83].

4.2.4. Sub-Saharan Africa

Cases of poisoning by pufferfish in the south-west Indian Ocean do not occur frequently, ~~therefore people are often unaware of the potential toxicity of these fish.~~ The most recent case involved an entire family in Reunion in 2013, following the consumption of *L. sceleratus*, fished by the father and cooked as a local dish called *carri* which involves the use of different parts mixed together, in such a way that might have favoured the general contamination with TTX. Since the island is a French department, the European legislation that prohibits the commercialization of specimens of the family Tetraodontidae and its derivatives is in force, but the inhabitants of the place do not seem to be aware of this~~, so it would be useful to implement information campaigns to raise awareness the population at risk~~ [52].

4.2.5. Oceania

In this region a presumed TTX poisoning was first documented when Captain James Cook and his crew, in 1774, stopped off the New Caledonia and decided to consume a soup made with liver and gonads of a locally purchased fish~~. The subsequent detailed description of the symptomatology allows hypothesizing that the food consumed was a~~

~~pufferfish~~ [84]. Although pufferfish intoxications in this area are described as rare, the risk of TTX poisoning exists given the presence of several species of pufferfish in many Australian coastal regions [2]. In fact, an interesting biodiversity was observed in the source of intoxication in Oceania:~~. In particular,~~ other than Tetraodontidae also Ostraciidae and Diodontidae (among which *Diodon hystrix*) were reported as responsible for human cases. Even though boxfish (family Ostraciidae) and porcupinefish (family Diodontidae) are considered as "non-toxic species" [85] in a study by Elshaer [86] TTX ~~has been~~was extracted from ovary and muscle of *D. hystrix*. Therefore, the toxicity of these species of Tetraodontiformes needs to be further clarified.

Similarly~~,~~ to Central-South America, the origin of the source of intoxication was always local and in most of the cases it involved products caught during recreational fishing sessions and consumed ~~together~~ with the family (Table 2SM)~~ (Maillaud et al. 2016; Tibbals 1988; Torda, Sinclair, and Ulyatt 1973; Trevett, Mavo, and Warrell 1997)~~.

4.2.6. North America

In North America TTX intoxications were exclusively caused by pufferfish. The most implicated genera were *Lagocephalus*, in particular *L. lunaris*, involved in cases after 1996, and *Arothron*, responsible for very dated cases occurred in Hawaii between 1903 and 1925 [1]. In addition, for 3 out of 13 cases generically attributed to pufferfish it is possible to hypothesize that the species involved was *L. lunaris* [33]. As in Oceania, a case of intoxication was related to the consumption of *D. hystrix* [87].

The 12 oldest intoxication occurred between 1903 and 1986 in Hawaii and in Florida, which caused at least 7 deaths, are unfortunately poorly detailed. More details are available for the 11 more recent poisonings~~, between~~ (1996–~~ and~~ 2014). All were caused by products imported from Asia. In 1996 in California 3 cooks were intoxicated by a ready-to-eat product made of *fugu* bought in Japan and illegally brought to the USA ([34].

Subsequently, 7 cases occurred between 2006 and 2007 were traced back to a Californian wholesaler who supplied local vendors and restaurants in different countries with products labelled as gutted and beheaded monkfish of Chinese origin. In 4 of these, substitution with *L. lunaris* (whose muscle contains TTX) was confirmed by molecular identification and, probably, this species was involved in all 7 cases [33]. Finally, in 2014 a pufferfish intoxication occurred in Virginia, in a person who had received a parcel from relatives in South Korea, [35~~https://www.foodsafetynews.com/2014/01/fda-investigating-puffer-fish-poisoning-in-virginia/#.W1WZ5NIzbIX~~]. This framework shows that the risk of TTX intoxication in the USA comes mainly from imported products, despite the stringent legislation in force. In fact, a single company is allowed to import *Takifugu rubripes* for restaurants. Moreover, as regards ~~consumption of~~ local pufferfishes, consumption of those caught in coastal waters of the mid-Atlantic (between New York and Virginia state) is admitted since these are considered free from the toxin, while the State of Florida currently has a ban on both commercial and recreational harvesting of pufferfish [31]. The ban was established after the largest outbreak due to pufferfish intoxication in the US history [88], which however was caused by ~~saxitoxin~~STX and not by TTX (these cases were not included in our analysis).

~~On the contrary, endemic pufferfish represented an important source of protein and income for the East Coast populations of the USA during the Second World War and in the following decades (Sibunka and Pacheco 1981). Despite the TTX poisonings recorded in Florida (Benson 1956; Black, Cox, and Horwitz 1978) the East Coast~~

~~pufferfish of the United States were considered as safe for a long time (Quilliam et al. 2002). However, between 2002 and 2004, 28 pufferfish poisonings occurred and were attributed to specimens caught in Florida (Bodager 2002; Landsberg et al. 2006), representing the largest outbreak due to pufferfish intoxication in the US history (Deeds et al. 2008). The responsible toxin was identified as saxitoxin and not TTX, therefore these cases were not included in our analysis. Prior to 2002, no toxicity from pufferfish originating from the region had ever been reported and the same 7 cases reported above in Florida had been caused by specimens caught outside this specific area (Deeds et al. 2008). Following this event, the FDA imposed a ban on the capture and consumption of local pufferfish in force only for certain counties on the east coast of the State of Florida, while the specimens fished in the Middle Atlantic remain fishable and tradable as non-toxic between the states of Virginia and New York (FDA, 2014https://www.fda.gov/food/recallsoutbreaksemergencies/safetyalertsadvisories/ucm085458.htm). However, a risk of TTX intoxication due to the presence of highly toxic~~ ~~*Sphoeroides* species is potentially present in the area Deeds et al. (2008).~~

4.2.7. Europe

~~All the 13 dated cases occurred in Europe were always due to the ingestion of imported mislabelled pufferfish. In addition, intoxications occurred in France due to mislabelling of fillets of pufferfish sold as burbot (*Lota lota*) (de Haro et al. 2008) and a mass hospitalization of the crewmembers of a tanker off Crete Island was reported, following the consumption of~~ ~~*L. sceleratus*~~~~. However, since it was not possible to obtain sufficient data (number of patients involved) on these cases, they were not included in the analysis.~~

~~As mentioned, t~~The 13 dated poisonings caused by pufferfish~~,~~ are all related to the consumption of ~~Asian~~ Taiwan imported frozen pufferfish, fraudulently labelled as anglerfish, ~~food~~ and all occurred Italy (Table 2SM)~~: 7 in Iesolo and 3 in Rome in 1977~~

~~(Pocchiari 1977) and 3 in Pavia in the following year (Viviani et al. 1978). The responsible product was frozen pufferfish, imported from Taiwan and fraudulently labelled as anglerfish (Pocchiari 1978), similarly to the intoxication occurred in France (de Haro et al. 2008)~~. In addition, a similar intoxication occurred in France due to mislabelling of fillets of pufferfish sold as burbot (*Lota lota*) [89] and a mass hospitalization of the crewmembers of a tanker off Crete Island was reported, following the consumption of *L. sceleratus.* However, since it was not possible to obtain sufficient data (number of patients involved) on these cases, they were not included in the analysis.

Interestingly, ~~T~~the remaining recent European case of ~~European~~ intoxication due the consumption of a marine gastropod caught in Portugal [13, 90] is~~, on the contrary,~~ due to a locally sourced product. This poisoning from *C. lampas lampas* is a very important event from an epidemiological point of view as it is the first confirmed case of TTX intoxication caused by a fishery product from the European coasts, and as it testif~~y~~ies~~ing~~ the presence of TTX also in the Atlantic Ocean [90], which was further confirmed by the study of M. J. Silva et al. [15] on gastropods from North Portugal. Subsequently, TTX was found in bivalves (*Mytilus edulis and Crassostrea gigas*) collected in the English Channel ~~between February 2013 and October 2014~~ [18, 91] and in oysters and mussels collected from different Dutch production areas in 2015 and 2016 [17]. Recently, Leão et al. [92], reported the occurrence of TTX associated to marine *Vibrio* spp. in bivalves from the Galician Rias, while Turner et al. [45] found high levels of TTX in a new invasive nemertean species in England. In the Mediterranean Sea, the toxin has been reported in specimens of *L. sceleratus* caught in the Aegean Sea in 2007 [39] and along the Spanish coast in 2014 [37], as well as in specimens of *Mytilus galloprovincialis* and *Venus verrucosa* caught in the seas of

Greece in different periods (2006-2012, 2012 and 2014) [19] and, more recently, in shellfish from Northern and Southern Italy [93-94]. These findings highlight the need of a new risk~~s~~ based approach to control this food safety issues, also considering that until now a maximum TTX level in seafood has not been established by the ~~current~~ European legislation [17]. Currently, EU regulation only manages the risk by prohibiting the marketing of fishery products obtained from fish of the Tetraodontidae families, Molidae, Diodontidae and Canthigasteridae [32], thus not yet considering the other product categories that could potentially carry the TTX.

~~It is likely that the presence of TTX was favoured by different factors such as global warming (Danovaro, Umani, and Pusceddu 2009) and the "Lessepsian" migration of tropical species, including pufferfish species, which transported TTX and TTX producing bacteria to new areas (Akyol et al. 2005; Bentur et al. 2008; Corsini et al. 2006; Katikou et al. 2009; Por 2012; Rambla-Alegre et al. 2017; M. J. Silva et al. 2012). In fact, until 2005 TTX distribution mainly affected the warm waters of Southeast Asia (Bane et al. 2016).~~

~~Such discovery inevitably has an impact on food safety, as it has determined the need to manage a risk linked to a new toxin previously not subject to adequate regulation (Rodriguez et al. 2008). In fact, there are no Health Based Guideline Values (HBGVs) for TTX worldwide and no~~a ~~maximum TTX levels in seafood in the EU~~ has nit been established by ~~the current European legislation (EFSA CONTAM Panel 2017)~~. ~~which~~ EU regulation ~~manages the risk only by prohibiting the marketing of fishery products obtained from fish of the Tetraodontidae families, Molidae, Diodontidae and Canthigasteridae (Reg. (CE) No. 853/2004), not considering the other product categories that could potentially carry the TTX.~~

5. Conclusions

The present study shows that different food products and geographical context influence the risk of TTX intoxication.

TTX poisoning is confirmed to be a main issue in South East and East Asia. In this geographical area most of the cases where described following the ingestion of all the seafood product categories (fish, gastropods, arthropods, cephalopods). Interestingly, it was the only geographical sub-area where intoxications from *C. rotundicauda* (arthropod) and *Hapalochlaena* spp. (cephalopod) were reported. In Oceania, Sub-Saharan Africa and Central-South America the poisoning cases were caused exclusively by pufferfish, with sporadic frequency and mainly during family consumption of locally caught specimens. In North America, where cases were described exclusively in the United States, the consumption of illegally imported or mislabeled Asian products was generally implicated. The same occurred for the few dated intoxications reported historically in Europe. However, the recent spread of TTX towards new marine environments, such as the Mediterranean Sea and the Atlantic Ocean, represent an emerging risk in Europe, in Middle East countries and North Africa, as confirmed by the recent cases of intoxication in these regions.

Even though, in view of the large geographical area and period of time analyzed, it is possible that a few cases reported in grey literature might have escaped the analysis, outcomes from this comprehensive global survey furnish an update scenario on TTX intoxication according to geographical area and the implicated seafood. It therefore represents a useful source of data to feed risk assessment by taking into account the changing environmental and anthropogenic factors. Consequently, risk management should be updated, also considering that there are no Health Based Guideline Values for TTX worldwide. Beside issuing updated regulation, increasing awareness of all the stakeholders, such as policy makers, food business operators and consumers is strongly needed.

~~Even though, in view of the large geographical area and period of time analysed, it is possible that a few cases reported in grey literature might have escaped the analysis, this work represents the first comprehensive global survey, providing epidemiological data useful for risk assessment.~~

~~TTX intoxication is confirmed to be a main issue in South East and East Asia, where most of the intoxications where described. Intoxications occurred in this sub-area derived from the widest variety of product categories: beside fish, which was common to all geographic areas investigated, most of the intoxications caused by marine gastropods occurred in South East and East Asia, which was also the only geographical sub-area where intoxications from *C. rotundicauda* (arthropod) and *Hapalochlaena* spp. (cephalopod) were reported.~~

~~In North America cases were described exclusively in the United States, mainly due to the consumption of illegally imported or mislabelled Asian products. Similarly, the few dated intoxications reported historically in Europe were all referable to mislabelled products imported from Asia. However, the present study highlights the spread of TTX towards new marine environments, as confirmed by the recent cases of intoxication, occurred in Europe (Spain), in Middle East countries (Israel and Lebanon) and North Africa (Egypt, Morocco and Tunisia). Therefore, there is a strong need to reassess the risk related to TTX intoxication, taking into account the changed environmental and anthropogenic factors.~~

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Contribution of authors

LG: study selection and data extraction and writing review; AM: bibliographic search, study selection and data extraction; DN: statistical analysis; VM: revision of the manuscript; LG: bibliographic search; AA: experimental design, supervising of all phases and writing review.

Declaration of interest statement

No conflict of interest to declare

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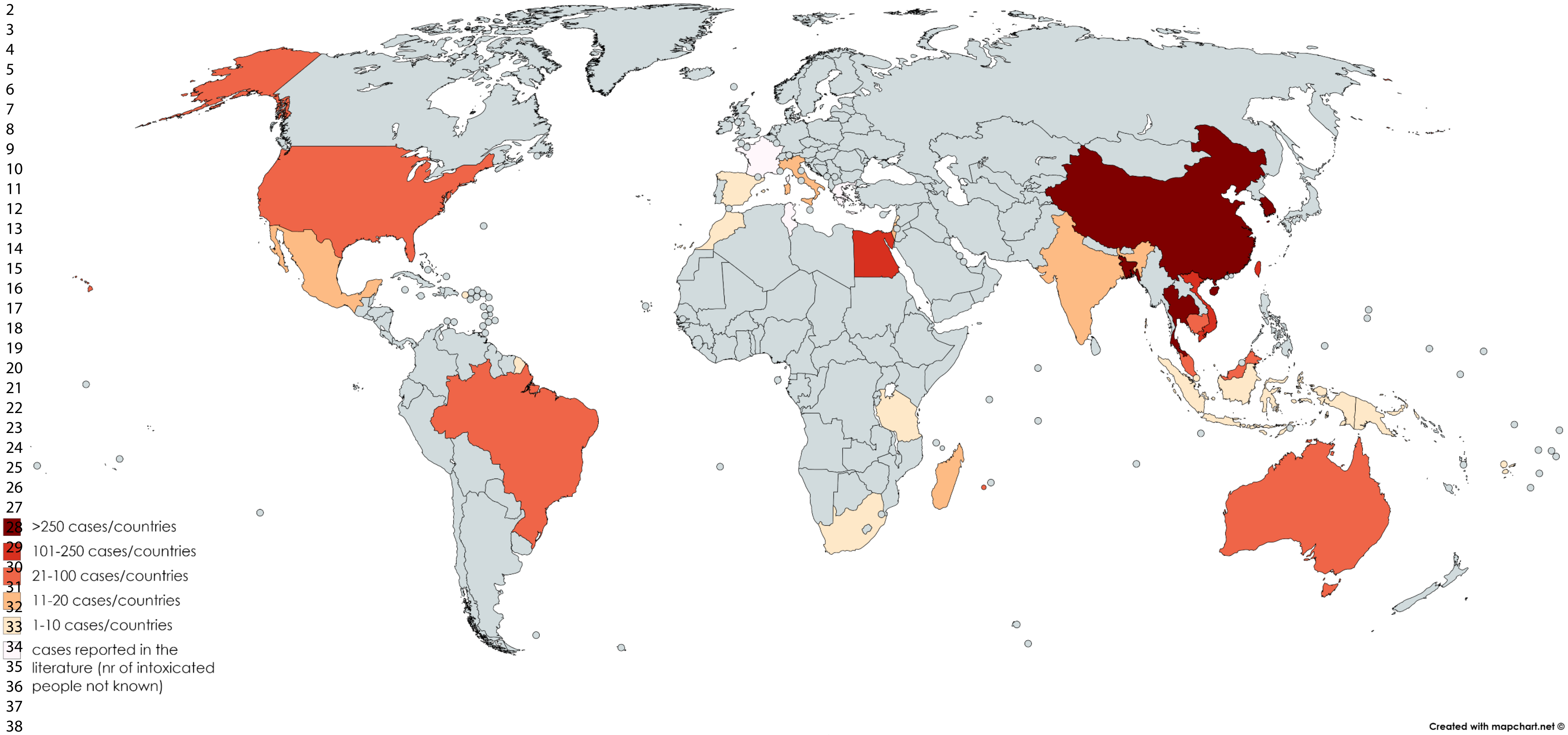
Figure captions

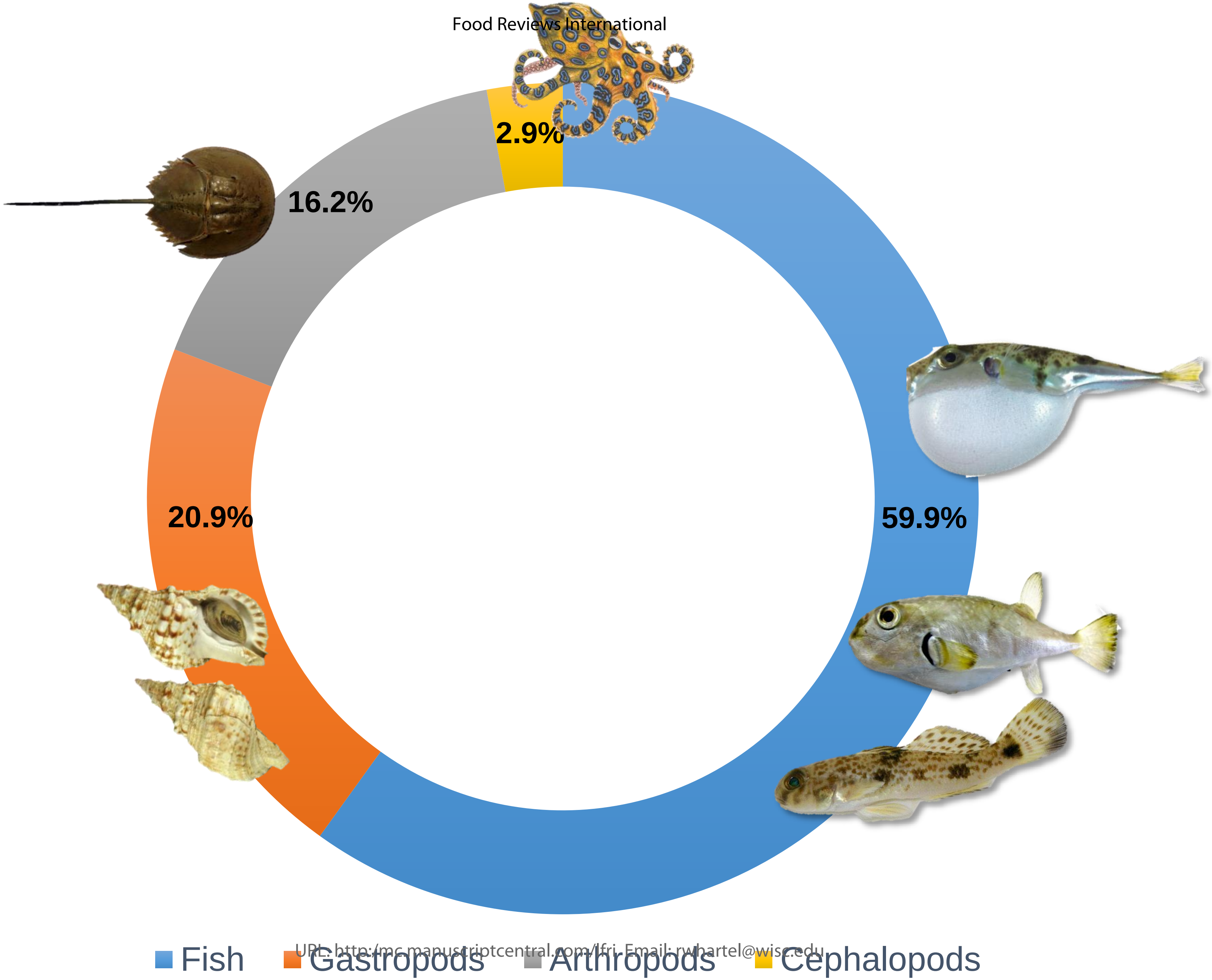
Fig. 1 Global map reporting the distribution per country of the cases included in the present study.

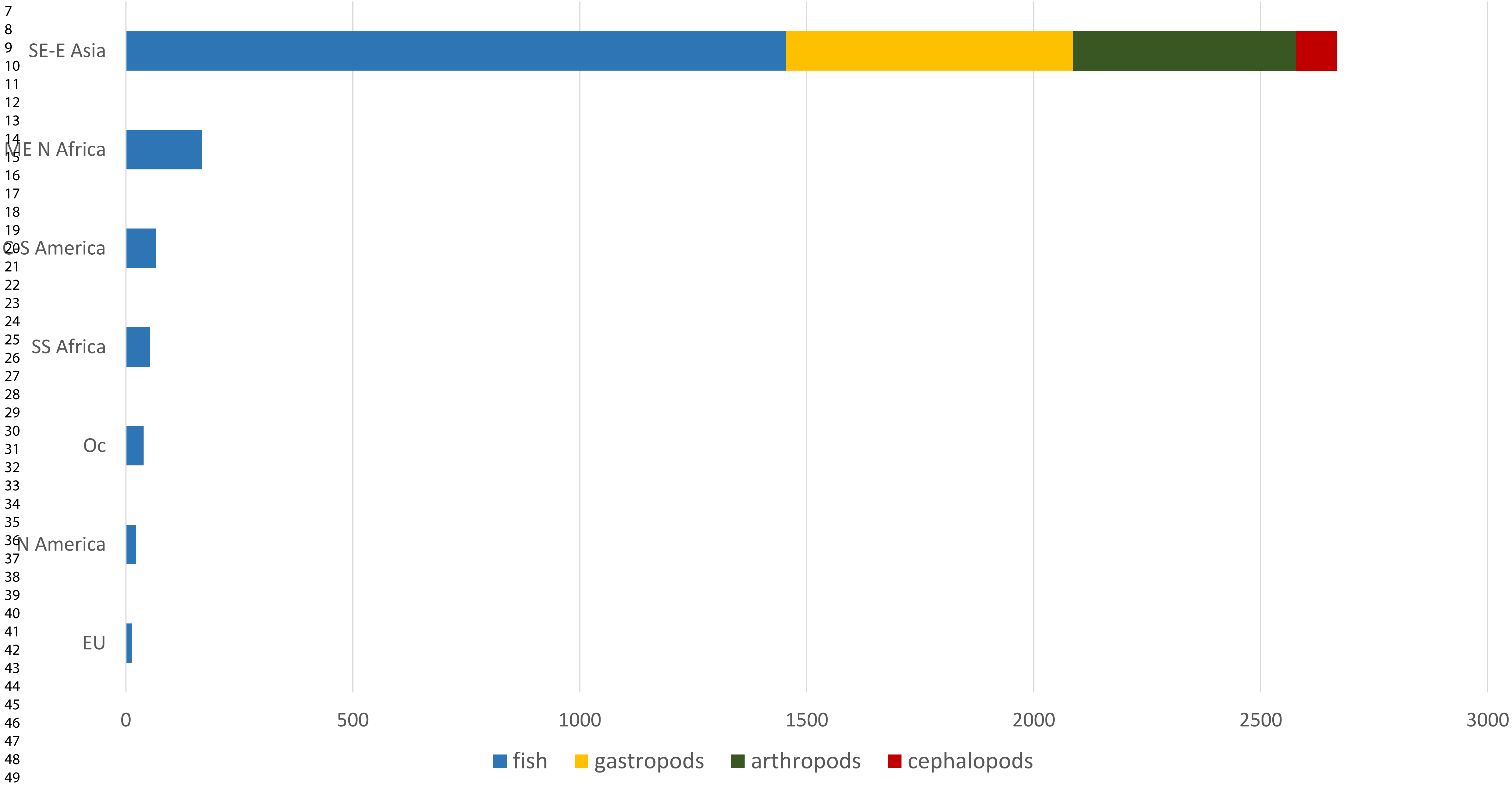
Fig. 2 Graphic representation of the seafood categories responsible for the case of intoxications collected in the present study.

Fig. 3 Distribution of the seafood categories responsible for the case of intoxications per sub area. SE-E Asia: South East and East Asia; ME-N Africa: Middle East and North Africa; C-S America: Central and South America; SS Africa: Sub-Saharan Africa; OC: Oceania; NAmerica: North America; EU: Europe.

Fig. 4 Most relevant fish anatomical part responsible for intoxications


>250 cases/countries
101-250 cases/countries
21-100 cases/countries
11-20 cases/countries
1-10 cases/countries
cases reported in the literature (nr of intoxicated people not known)
Created with mapchart.net ©


2.9%
16.2%
59.9%
20.9%
Fish
Gastropods
Arthropods
Cephalopods


SE-E Asia
ME N Africa
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0
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fish
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arthropods
cephalopods

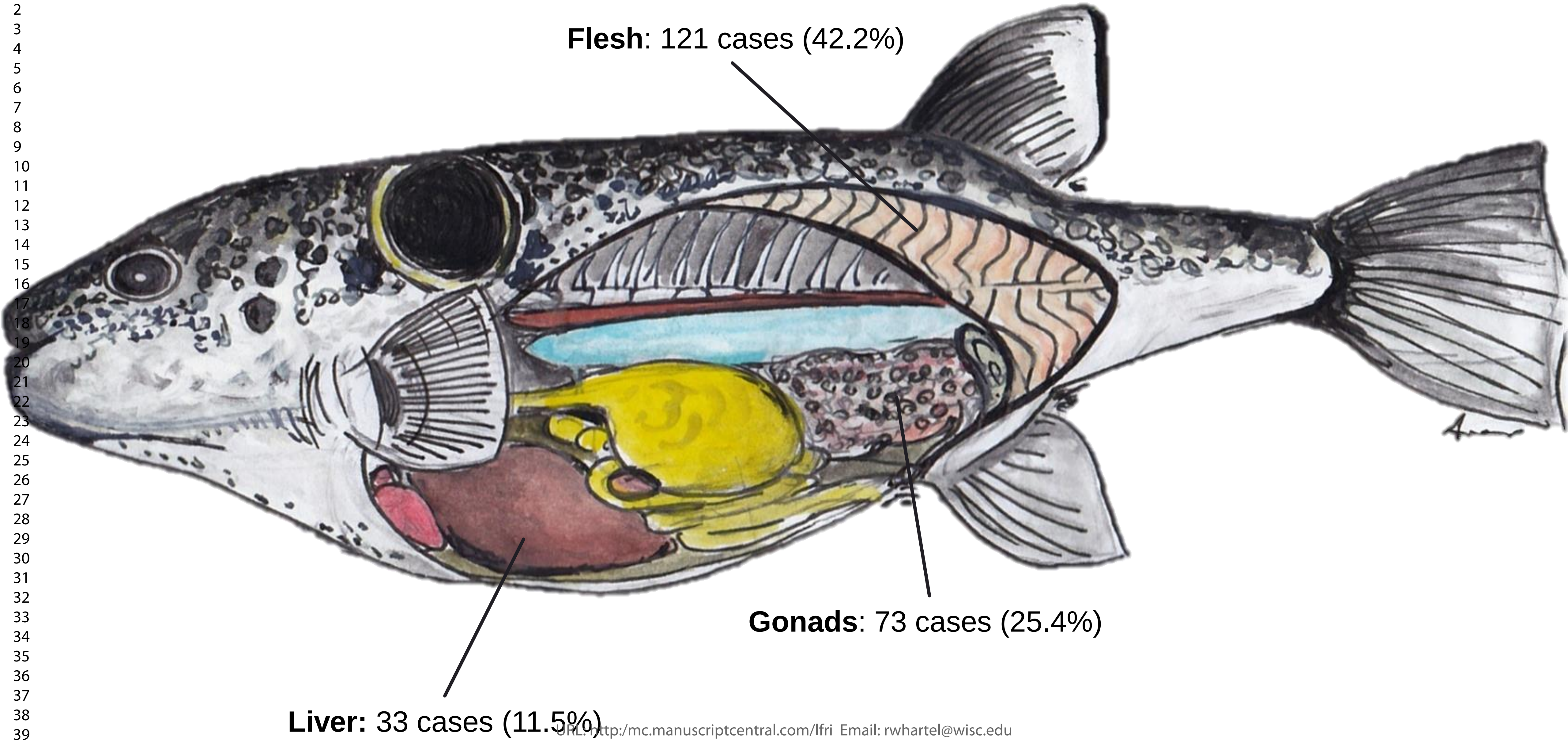
Flesh: 121 cases (42.2%)
Gonads: 73 cases (25.4%)
Liver: 33 cases (11.5%)

Table 1. Details of the total number of cases of human intoxication by TTX worldwide, divided in non-fatal and fatal cases, according to the different geographical regions and to the different sources of intoxications. ᵃin the case of USA (sub-area North America); *minimum number

Sub-area (n countries/ states)	**Country/State**ᵃ	**N of non-fatal cases (% of the total number)**	**N of fatal cases (% of the total number)**	**Total n of cases**	**Source of intoxication (total n of cases/n of fatalities)**			
					Fish	**Gastropods**	**Arthropods**	**Cephalopods**
South-East and East Asia (11)	India	10 (50%)	10 (50%)	20	generic pufferfish (9/2)			
					Chelonodon patoca (3/2)			
					Tetrodon spp. (8/6)			
	Bangladesh	268 (79.8%)	68 (20.2%)	336	generic pufferfish (106/25)			
					Arothron stellatus (48/7)			
					Takifugu oblongus (127/19)			
					Tetrodon spp. (55/17)			
	Thailand	765 (97.1%)	23 (2.9%)*	788			*Carcinoscorpius rotundicauda* (457/8)	
					generic pufferfish (325/15)			
					Tetrodon spp. (6/0)			
	Malaysia	74 (85.1%)	13 (14.9%)*	87			*Carcinoscorpius rotundicauda* (30/3)	
					generic pufferfish (57/10)			
	Singapore	21~~5~~ (100%)	0	21~~5~~	generic pufferfish (34/0)			
					Sphoeroides maculatus (17/0)			
					Arothron reticularis (1/0)			
	Indonesia	0	6 (100%)	6	generic pufferfish (6/6)			
	Cambodia	48 (84.2%)	9 (15.8%)	57	generic pufferfish (57/9)			
	Vietnam	96 (91.4%)	9 (8.6%)	105		*Nassarius* spp. (7/3)		
						Natica fasciata (5/0)		
								Hapalochlaena fasciata (87/2)
					generic pufferfish (6/4)			
	Taiwan	222 (89.5%)	26 (10.5%)*	248	unidentified fish (64/8)			
					Chelonodon patoca (1/1)			
						Nassarius spp. (64/5)		
					Lagocephalus lunaris (19/3)			
						Oliva spp. (1/0)		

								Hapalochlaena fasciata (2/0)
					Takifugu niphobles (6/0)			
					Gobiidae (11/0)			
					generic pufferfish (71/9)			
						unknown gastropod (8/0)		
						Neverita didyma (1/0)		
	China	655~~71~~ (95.2~~3~~%)	33 (4.~~7~~8%)	~~704~~688	~~*Sphoeroides maculatus* (16/0)~~			
					Gobiidae (22/0)			
						Nassaridae (547/23)		
					generic pufferfish (114/9)			
							Carcinoscorpius rotundicauda (5/1)	
	South Korea	230 (73.7%)	82 (26.3%)	312	*Lagocephalus lunaris* (2/0)			
					generic pufferfish (307/81)			
					unidentified fish (3/1)			
	Subtotal South-East and East Asia	**2389 (89.5%)**	**279 (10.5%)**	**2668**	**1454/234**	**633/31**	**492/12**	**89/2**
Middle East and North Africa (4)	Israel	16 (100%)	0	16	*Lagocephalus sceleratus* (16/0)			
	Lebanon	2 (100%)	0	2	*Lagocephalus sceleratus* (2/0)			
	Egypt	120 (81.6%)	27 (18.4%)	147	generic pufferfish (59/14)			
					Lagocephalus sceleratus (76/12)			
					unidentified fish (12/1)			
	Morocco	2 (66.7%)	1 (33.3%)	3	Tetraodontidae (gen. pufferfish) (3/1)			
	Subtotal Middle East and North Africa	**140 (83.3%)**	**28 (16.7%)**	**168**	**168/28**			
Centre-South America (4)	Brazil	37 (90.2%)	4 (9.8%)	41	generic pufferfish (28/3)			
					Sphoeroides spp. (13/1)			
	French Guyana	4 (80%)	1 (20%)	5	unidentified fish (3/1)			
					Sphoeroides testudineus (2/0)			
	Mexico	18 (90%)	2 (10%)*	20	generic pufferfish (18/NR)			
					Sphoeroides spp. (2/2)			

	Puerto Rico	1 (100%)	0	1	generic pufferfish (1/0)
	Subtotal Centre-South America	**60 (89.6%)**	**7 (10.4%)**	**67**	**67/7**
Sub-Saharan Africa (4)	Madagascar	12 (70.6%)	5 (29.4%)	17	*Arothron* spp. (*A. hispidus* 4) (17/5)
	Tanzania (Zanzibar)	0	1 (100%)	1	generic pufferfish (1/1)
	La Reunion Island	30 (90.9%)	3 (9.1%)	33	*Lagocephalus sceleratus* (10/0)
					generic pufferfish (23/3)
	South Africa	0	2 (100%)	2	generic pufferfish (2/2)
	Subtotal Sub-Saharan Africa	**42 (79.2%)**	**11 (20.8%)**	**53**	**53/11**
Oceania (3)	Australia	28 (90.3%)	3 (9.7%)	31	generic pufferfish (17/1)
					Lagocephalus sceleratus (3/0)
					Ostraciidae (4/0)
					Diodontidae (1/0)
					Arothron spp. (*Arothron nigropunctatus*) (4/1)
					Sphoeroides spp. (*S. liosomus*) (1/1)
					Tetroctenas glaber (1/0)
	New Guinea	1 (33.3%)	2 (66.7%)	3	*Diodon hystrix* (3/2)
	Fiji	4 (80%)	1 (20%)	5	*Diodon hystrix* (5/1)
	Subtotal Oceania	**33 (84.6%)**	**6 (15.4%)**	**39**	**39/6**
North America (7)	California	5 (100%)	0*	5	generic pufferfish (5/0)
	Illinois (Chicago)	2 (100%)	0	2	*Lagocephalus lunaris* (2/0)
	Minnesota (Minneapolis)	2 (100%)	0	2	*Lagocephalus lunaris* (2/0)
	New Jersey	1 (100%)	0*	1	generic pufferfish (1/0)
	Virginia	1 (100%)	0	1	generic pufferfish (1/0)
	Hawaii	1 (20%)	4 (80%)	5	*Diodon hystrix* (1/0)
					Arothron spp. (4/4)
	Florida	4 (57.1%)	3 (42.9%)*	7	*Sphoeroides testudineus* (1/1)
					generic pufferfish (6/2)
	Subtotal North America	**16 (69.6%)**	**7 (30.4%)**	**23**	**23/7**
Europe	Italy	10 (76.9%)	3 (23.1%)	13	generic pufferfish (13/3)

(2	Spain	1 (100%)	0	1		*Charonia lampas* (1/0)		
	Subtotal Europe	**11 (78.6%)**	**3 (21.4%)**	**14**	**13/3**	**1/0**		
	Total	**2691 (88.7%)**	**341 (11.3%)**	**3032**	**1817**	**634**	**492**	**89**

Table 2 Fatality rates across continents and geographical sub-regions. Significant differences are evidenced in the column Difference: same letters indicate non statistically different proportions.

Continent	Fatality rate (%)	Difference	Statistics
Asia	10.5	A	X^2=18,4 p=0,01
Africa	19.2	B	
America	15.6	B	
Oceania	15.4	B	
Europe	21.4	B	
Overall mean	16.4		
Sub-areas	**Fatality rate (%)**	**Difference**	**Statistics**
South-East and East Asia	10.5	A	X^2=21,8 p=0,001
Middle East and North Africa	16.7	A	
Sub-Saharan Africa	20.8	B	
North America	30.4	B	
Centre and South America	10.4	A	
Europe	21.4	B	
Oceania	15.4	A	
Overall mean	17.9		

Table 3. Details of the source of intoxication subdivided by taxonomic groups

Taxonomic group and species	**Total n of cases**	**%**	**Fatalities**	**%**
Fish	**1817**	**59.9**	**296**	**86.8**
Generic "pufferfish"	1239~~40~~	68.3	200	67.6
Takifugu spp. (Tetraodontidae, Tetraodontiformes)	133	7.3	19	6.4
Lagocephalus sceleratus (Tetraodontidae, Tetraodontiformes)	107	5.9	12	4.1
Lagocephalus lunaris (Tetraodontidae, Tetraodontiformes)	25	1.4	3	1.0
Tetrodon spp. (Tetraodontidae, Tetraodontiformes)	69	3.8	23	7.8
Arothron spp. (Tetraodontidae, Tetraodontiformes)	74	4.1	17	5.7
Sphoeroides spp. (Tetraodontidae, Tetraodontiformes)	36~~5~~	1.9	5	1.7
Chelonodon patoca (Tetraodontidae, Tetraodontiformes)	4	0.2	3	1.0
Tetroctenas glaber (Tetraodontidae, Tetraodontiformes)	1	0.1	0	0.0
Diodon spp. (Diodontidae, Tetraodontiformes)	10	0.6	3	1.0
Ostraciidae (Tetraodontiformes)	4	0.2	0	0.0
Total Tetraodontiformes	1703	93.7	285	96.3
Gobiidae (Perciformes)	33	1.8	0	0.0
Unidentified fish	82	4.5	11	3.7
Gastropod	**634**	**20.9**	**31**	**9.1**
Nassaridae, Neogastropoda	618	97.5	31	100
Natica fasciata (Naticidae, Littorinimorpha)	5	0.8	0	0.0
Charonia lampas (syn. *Lampas lampas*) (Ranellidae, Littorinimorpha)	1	0.2	0	0.0
Oliva spp. (Olividae, Neogastropoda)	1	0.2	0	0.0
Neverita didyma (Naticidae, Littorinimorpha)	1	0.2	0	0.0
Unknown species	8	1.3	0	0.0
Arthropod	**492**	**16.2**	**12**	**3.5**
Carcinoscorpius rotundicauda (Limulidae, Xiphosuridae)	492	100	12	100
Cephalopod	**89**	**2.9**	**2**	**0.6**
Hapalochlaena fasciata (Octopodidae, Octopoda)	89	100	2	100
Total	**3032**		**341**	

Table 1SM. Toxicological tests used in the studies included in the analysis

Toxicological analysis	**N**
No analysis	2641
Mouse Bioassay (MBA)	102*
MBA and High-Performance Liquid Chromatography (HPLC)	67*
MBA and Liquid Chromatography-Mass Spectrometry (LC-MS)	12
MBA, HPLC and Thin-layer chromatography (TLC)	43
MBA, HPLC and LC-MS	8
MBA, HPLC and GC-MS	12
MBA, HPLC, LC-MS and GC-MS	1
HPLC	38
LC-MS	34
GC-MS	7
LC-MS and GC-MS	6
TLC, electrophoresis and HPLC	7
Enzyme-linked immunosorbent assays (ELISA)	38
TTX confirmed but test not specified	16

*test on samples collected from the same seashore area of the poisoning (n=8 in MBA and HPLC and n=42 in MBA)

Table 2SM. Data on the number of cases and fatalities in relation to the geographical region, the source of intoxication, the origin of the source, the year and information on the identification of TTX.

Geographical region and country/state	**Source of intoxication**	**Local**	**Imported**	**n.a.**	**Years**	**TTX identified**	**Number of cases**	**Number of fatalities**	**References**
Europe									
Italy	generic pufferfish (F)	0	13	0	1977-1978	Yes	13	3	Viviani et al., 1978; Pocchiari 1977
Spain	*Charonia lampas* (G)	1	0	0	2007	Yes	1	0	Fernandez-Ortega et al., 2010; Rodriguez et al., 2008
North America									
California	generic pufferfish (F)***	0	5	0	1996, 2006	No	5	0[a]	CDC, 1996; Cohen et al., 2009
Illinois (Chicago)	*Lagocephalus lunaris* (F)	0	2	0	2007	Yes	2	0	Cohen et al., 2009
Minnesota (Minneapolis)	*Lagocephalus lunaris* (F)	0	2	0	2014	Yes	2	0	Cole et al., 2014
New Jersey	generic pufferfish (F)***	0	1	0	2007	No	1	0[a]	Cohen et al., 2009
Virginia	generic pufferfish (F)	0	1	0	2014	No	1	0	Report FDA, 2014
Hawaii	*Diodon hystrix* (F)	0	0	1	1986	No	1	0	Sisms and Ostman, 1986
	Arothron spp. (F)	0	0	4	1903-1925	No	4	4	Helfrich, 1963
Florida	*Sphoeroides testudineus* (F)	0	0	1	1954-1955	No	1	1	Benson, 1956
	generic pufferfish (F)	0	0	6	1951-1974	No	6	2[a]	Benson, 1956; Philips and Brady, 1953
Centre-South America									
Brasil	generic pufferfish (F)	0	0	28	1984-2009	No	28	3	Silva et al., 2010; Haddad et al., 2004
	Sphoeroides spp. (F)	12	0	1	n.a., 2008	No	13	1	Neto et al., 2010; de Souza et al., 2014 ; Ferreira et al., 2010.
French Guyana	unidentified fish (F)	0	0	3	n.a.	Yes	3	1	Villa et al., 2010
	Sphoeroides testudineus (F)	2	0	0	1990	No	2	0	Hommel et al., 1992
Mexico	generic pufferfish (F)	0	0	18	1970-1996	No	18	2[a]	Sierra-Beltran et al., 1998
	Sphoeroides spp. (F)	0	0	2	1995	No	2	2	Ochoa et al., 1997
Puerto Rico	generic pufferfish (F)	0	0	1	n.a.	No	1	0	Joy-Sobrino et al., 1985
Oceania									

Australia	generic pufferfish (F)	5	0	12	2001-2006, n.a. (5)	Yes (7, Isbiter et al., 2002)	17	1	Field et al., 1998; Isbister et al., 2002 ; Maillaud et al., 2016 ; Torda et al., 1973
	Lagocephalus sceleratus (F)	3	0	0	1996	No	3	0	Ellis and Jelinek, 1997
	Ostraciidae (F)	0	0	4	1996	No	4	0	Maillaud et al., 2016
	Diodontidae (F)	0	0	1	2007	No	1	0	Maillaud et al., 2016
	Arothron spp. (Arothron nigropunctatus) (F)	4	0	0	2014	No	4	1	Maillaud et al., 2016
	Sphoeroides spp. (*S. liosomus*) (F)	1	0	0	1950	No	1	1	Sutherland, 1985
	Tetroctenas glaber (F)	1	0	0	n.a.	No	1	0	Tibbalds, 1988
New Guinea	*Diodon hystrix* (F)	3	0	0	n.a.	No	3	2	Trevett et al., 1997
Fiji	*Diodon hystrix* (F)	0	0	5	1967	No	5	1	Sorokin, 1973
Middle East and North Africa									
Israel	*Lagocephalus sceleratus* (F)	15	0	1	2005-2008 (13), n.a.(3)	No	16	0	Bentur et al., 2008; Eisenmann et al., 2008 ; Kheifets et al., 2012
Lebanon	*Lagocephalus sceleratus* (F)	0	0	2	2008	No	2	0	Awada et al., 2010; Chamandi et al., 2009
Egypt	generic pufferfish (F)	11	0	48	2008-2010 (48); n.a. (11)	No	59	14	Zaki, 2004; El Masry and Fawzi, 2011
	Lagocephalus sceleratus (F)	1	0	75	2006, 2010	No	76	12	El Masry and Fawzi, 2011
	unidentified fish (F)	0	0	12	2008, 2010	No	12	1	El Masry and Fawzi, 2011
Morocco	Tetraodontidae (F)	0	0	3	n.a.	No	3	1	Ababou et al., 2000
Sub-Saharan Africa									
Madagascar	*Arothron* spp. (*A. hispidus* 4) (F)	0	0	17	1993-1998	No	17	5	Ravaonindrina et al., 2001; Champetier de Ribes et al., 19998
Tanzania (Zanzibar)	generic pufferfish (F)	0	0	1	1967	No	1	1	Chopra, 1967
La Reunion Island	*Lagocephalus sceleratus* (F)	10	0	0	2013	Yes	10	0	Puech et al., 2014
	generic pufferfish (F)	0	0	23	1950-1985	No	23	3	Quod et al., 1990
South Africa	generic pufferfish (F)	0	0	2	1845	No	2	2	Mills and Passmore, 1988; Hwang and Noguchi, 2007

Asia									
India	generic pufferfish (F)	0	0	9	2007-2008; n.a.	No	9	2	Behera et al., 2008; Chandra Sekaran et al., 2010
	Chelonodon patoca (F)	3	0	0	1954	No	3	2	Jones, 1956
	Tetrodon spp. (F)	6	0	2	1942-1950	No	8	6	Jones, 1956
Bangladesh	generic pufferfish (F)	43	0	63	2001-2014	Yes (10, Islam QT et al., 2011)	106	25	Islam QT et al., 2011; Islam MS et al., 2011 ; Chowdury et al., 2007 ; Chowdury, Hasan et al., 2007
	Arothron stellatus (F)	48	0	0	2008	No	48	7	Islam QT et al., 2011
	Takifugu oblongus (F)	127	0	0	1998-2008	Yes (38, Islam QT et al., 2011, 8 Mahmud et al., 1999)	127	19	Islam QT et al., 2011; Ahmed, 2006 ; Mahmud et al., 1999
	Tetrodon spp. (F)	29	0	26	1988-1996	No	55	17	Mahmud et al., 2000
Thailand	*Carcinoscorpius rotundicauda* (A)	0	0	457*	1994-2014	No	457	8	Kanchanapongkul, 2008; Joob et al., 2015
	generic pufferfish (F)	at least 140	0	185	1989-2008, n.a. (30)	No	325[a]	15[a]	Chulanetra et al., 2011; Samitsuwan et al., 2005; Kanchanapongkul, 2001 ; Kanchanapongkul, 2009; Kanchanapongkul and Tatraphon, 1993
	Tetrodon spp. (F)	6	0	0	1988	No	6	0	Laobripathr et al., 1990
Malaysia	*Carcinoscorpius rotundicauda* (A)	30	0	0	2011	Yes (7)	30	3	Suleiman et al., 2017
	generic pufferfish (F)	26	0	31	1987-2008; n.a.(5)	No	57	10[a]	Chua and Chew, 2009; Loke and Tan, 1997; Chan and David, 1987, Lyn 1985
Singapore	generic pufferfish (F)	0	0	34	1982 (1); n.a. (3)	No	34	0	Phua, 2013; Yong et al., 2013; Tan, 1980 ~~; Chew et al., 1983~~
	Sphoeroides maculatus (F)	0	0	1	1982	No	1	0	Chew et al., 1983
	Sphoeroides maculatus (F)	0	0	16	n.a.	No	16	0	Chew et al., 1984

	Arothron reticularis (F)	0	0	1	n.a.	No	1	0	Tambyah et al., 1994
Indonesia	generic pufferfish (F)	6	0	0	2001	No	6	6	Kungsuwan et al., 2001
Cambodia	generic pufferfish (F)	0	0	57	2003-2007	No	57	9	Ngy et al., 2008
Vietnam	*Nassarius* spp. (G)	7	0	0	2006-2007	Yes (12, Ha & Sato, 2010)	7	3	Ha and Sato, 2010
	Natica fasciata (G)	5	0	0	2007		5	0	Ha and Sato, 2010
	Hapalochlaena fasciata (C)	87	0	0	2004	No	87	2	Williams, 2008
	generic pufferfish (F)	0	0	6	n.a.	No	6	4	Cong and Tuan, 2006
Taiwan	unidentified fish (F)	30	0	34	n.a. (30), 1988-2000	Yes (23, Hwang, Cheng et al., 1995)	64	8	Hwang and Noguchi, 2007; Hwang and Lin, 2012; Hwang, Cheng et al., 1995; Chi and Wu, 2001; Deng et al., 1991
	Chelonodon patoca (F)	1	0	0	2009	Yes	1	1	Wu et al., 2011
	Nassarius spp. (G)	24	0	40**	1994-2012	Yes (3, Jen et al., 2008 ; 1, Lin et al., 2013 ; 2 Liu et al., 2004 ; 5 Hwang Shiu et al., 2002 ; 26 Hwang et al., 1995; 17 Yang et al., 1995 ; 6 Hwang et al., 2005 e	64	5^{a}	Lin et al., 2013; Yang et al., 1995; Hwang et al., 1995; Hwang et al., 2005; Yin et al., 2005 ; Hwang Shiu et al., 2002; Liu et al., 2004; Jen et al., 2008

						Yin et al., 2005)			
	Lagocephalus lunaris (F)	6	0	13*	1988-2008	Yes (6, How et al., 2003; 1 Hsieh et al., 2003 ; 5 Hwang et al., 2002; 3 Wu et al., 2008)	19	3^{a}	Wu et al., 2008; Yang, Liao and Deng 1996; Hwang et al., 2002; Hsieh et al., 2003; How et al., 2003; Tsai et al., 2006
	Oliva spp. (G)	0	0	1	2002	Yes	1	0	Hwang et al., 2003
	Hapalochlaena fasciata (C)	0	0	2*	2010	Yes	2	0	Wu et al., 2014
	Takifugu niphobles (F)	5	0	1	n.a.; 2000 (5)	Yes (5, Hsieh et al., 2002)	6	0	Hsieh et al., 2002; Chen et al., 2010
	Gobidae (F)	2	0	8	1994-1998	Yes (1 Lan et al., 1999)	11	0	Lan et al., 1999; Lin et al., 1999 ; Yang, Liao and Deng, 1996 ; Hwang and Noguchi, 2007 ; Lin and Hwang, 2012
	generic pufferfish (F)	0	0	71	1988-2003	No	71	9	Yang, Liao and Deng, 1996; Hwang & Noguchi, 2007; Lin and Hwang, 2012
	unknown gastropod (G)	0	0	8	2009	No	8	0	Lin et al., 2013
	Neverita didyma (G)	0	0	1	2000	Yes	1	0	Shiu et al., 2003
China	~~*Sphoeroides maculatus* (F)~~	~~0~~	~~0~~	~~16~~	~~n.a.~~	~~No~~	~~16~~	~~0~~	~~Chew et al., 1984~~
	Gobidae (F)	22	0	0	2012	Yes	22	0	You et al., 2015
	Nassaridae (G)	340**	0	207..0.0	1977-2005	Yes (31, Sui et al., 2002)	547	23	Shui et al., 2003; Sui et al., 2002; Takatani et al., 2005; Zhang et al., 2007 ; Wang et al., 2008
	generic pufferfish (F)	14	0	100	1992-2007; n.a.(10)	Yes (2, Chen & Huang,	114	9	Liu et al., 2005; Sun et al., 1994 ; Lau et al., 1995 ; Chen

						2013; 4 Wan et al., 2007)			& Huang, 2013 ; Wan et al., 2007 ; Liu et al., 2011
	Carcinoscorpius rotundicauda (A)	5	0	0	2014	Yes	5	1	Huang et al., 2016
South Korea	*Lagocephalus lunaris* (F)	0	0	2*	n.a.	No	2	0	Wi, 2013
	generic pufferfish (F)	0	0	307	1971-2011; n.a. (1)	No	307	81	Hyun et al., 2011; Kim et al., 2003; Lee & Kim, 1987 ; Mun et al., 1998 ; Wi, 2012
	unidentified fish (F)	3	0	0	2010	Yes	3	1	Cho et al., 2012

[a]minimum number; *considering its geographical distribution, the origin may be considered local; **considering the local tradition of eating fresh nassariids, the origin may be considered local; ***two cases in California in 2006 and one in New Jersey in 2007 probably due to *Lagocephalus lunaris.*

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Table 3SM: Toxicity resulting from *mouse bioassay* (MBA) in fish and gastropods reported in literature.

Reference	**Fish**	**Location**	**Number of intoxicated**	**Number of fatalities**	**Toxicity resulting from *mouse bioassay* (MBA)**
Puech et al., 2014	*Lagocephalus sceleratus*	La Reunion	10	0	Liver: 95 MU/g; Flesh: 5 MU/g
Ahmed et al., 2006	*Takifugu oblongus*	Bangladesh	36	7	Skin: 13.2–18.9 MU/g; Flesh: 2.7–4.4 MU/g Liver: <2.0–4.9 MU/g Gonads: <2.0–132.0 MU/g Viscera: 14.8–37.0MU/g
Mahmud et al., 1999	*Takifugu oblongus*	Bangladesh	8	5	Eggs: 24.5-323.8 MU/g Other tissues: <2-21.3 MU/g
Laobhripatr et al., 1990	*Tetraodon fangi*	Thailand	6	0	Skin: 209-2268 MU/g Gonads: 0-712 MU/g Flesh: 5-457 MU/g Liver: 19-225 MU/g Intestine: 21-224 MU/g Total specimen toxicity: 562-3070 MU
Deng et al., 1991	Pesce non identificato	Taiwan	30	1	Two food remains: 54 MU/g e 287 MU/g
Hsieh et al., 2003	*Lagocephalus lunaris*	Taiwan	1	0	Dried eggs: 3450 MU/g
Hwang et al., 2002°	*Lagocephalus lunaris*	Taiwan	5	0	Dried fillet: 253 MU/g
Hsieh et al., 2002	*Takifugu niphobles*	Taiwan	5	0	Coocked liver: 280±20 MU/g; Liver (fished specimens): Range 840±30-1810±30 MU/g Eggs: Range 870±10-1400±110 MU/g Flesh: Range 27±4-54±6 MU/g
Lan et al., 1999; Hwang e Noguchi, 2007	*Yongehichtys nebulosus*	Taiwan	1	0	Flesh: 25 MU/g
Lin et al., 1999	*Yongehichtys nebulosus*	Taiwan	2	0	Mean Value (Maximum value) Flesh: 117±142 MU/g (394); Skin: 124±69 (282) MU/g; Pinne: 360±162 MU/g (654);

					Testa: 368±237 MU/g (662); Viscera: 285±170 MU/g (624); Eggs 311±169 (510) MU/g. Total toxicity range of specimens: 5150±1510 MU
Yang et al., 1996	*Lagocephalus lunaris*	Taiwan	2	1	Flesh: 120 MU/g;
“	*Lagocephalus lunaris*	Taiwan	2	1	Eggs: 1200 MU/g; Flesh: 45 MU/g
“	Generically puffer fish	Taiwan	2	0	Eggs: 1100 MU/g
“	Generically puffer fish	Taiwan	3	1	Flesh: 150 MU/g
“	Generically puffer fish	Taiwan	4	0	Eggs: 150 MU/g
Chen et al., 2010	*Takifugu niphobles*	Taiwan	1	0	Eggs: 300 MU/g
Wu et al., 2008	*Lagocephalus lunaris*	Taiwan	3	NR	Eggs: 425±80 MU/g
Hwang et al., 1995°	Unidentified fish	Taiwan	2	1	Flesh 45 MU/; Skin 150 MU/g; Eggs 1,200 MU/g
“	Unidentified fish	Taiwan	5	1	Flesh 120 MU/g
“	Unidentified fish	Taiwan	2	1	Eggs: 1100 MU/g
“	Unidentified fish	Taiwan	3	1	Flesh: 150 MU/g
“	Unidentified fish	Taiwan	4	0	Eggs: 150 MU/g
Reference	**Gastropod**	**Location**	**Number of intoxicated**	**Number of fatalities**	**Toxicity resulting from *mouse bioassay* (MBA)**
Fernandez-Ortega et al., 2010; Rodriguez et al., 2008	*Charonia lampas lampas*	Spain	1	0	Digestive gland: 1432* MU/g; Flesh: 8.48* MU/g.
Ha e Sato, 2012	*Nassarius* spp.	Vietnam	3	2	Soft tissues: 70 MU/g
“	*Nassarius* spp.	Vietnam	5	0	<10 MU/g TTX and STX
“	*Nassarius* spp.	Vietnam	4	1	<10 MU/g TTX and STX
Jen et al., 2007	*Nassarius* spp.	Taiwan	1	0	Flesh: 645 MU/g; Digestive gland: 540 MU/g TTX and PSP
Jen et al., 2008	*Niotha clathrata*	Taiwan	3	0	Digestive gland mean value (maximum value): 353.93±135 (618*) MU/g; Flesh: 179.77±89.9 (393*) MU/g; Mean total toxicity of specimens: 202.24±135* MU.

Liu et al., 2004	*Nassarius papillosus* e *Nassarius gruneri*	Taiwan	2	1	Two specimens: 320 and 386 MU/g
Hwang et al., 2002b	*Zeuxis sufflatus* e *Niotha clathrata*	Taiwan	5	0	Digestive gland mean value (maximum value): 1117±477 (2310) MU/g and 683±113 (804) MU/g respectively in two species; Other tissues: 497±258 (1020) MU/g and 289±169 (525) MU/g respectively in two species;
Hwang et al., 2003	Olividae	Taiwan	1	0	*O. miniacea*: 18 MU/g; *O. mustelina*: 10 MU/g; *O. hirasei*: 27 MU/g
Hwang et al., 1995b	*Niotha clathrata* e *Zeuxis scalaris*	Taiwan	26	NR	Mean total toxicity of specimens of *Niotha* spp.: 150±126 MU e 345±192 MU; Mean total toxicity of specimens of *Z. scalaris:* 13±9 MU e 98±46 MU
Yang et al., 1995	*Nassarius conoidalis* e *Nassarius castus*	Taiwan	17	1	Mean total toxicity of specimens: 150±126 MU in *Nassarius conoidalis;* 13±9 MU in *Nassarius castus*
Lin et al., 2013	*Nassarius papillosus*	Taiwan	3	1	Mean total toxicity of specimens: 1044±706 MU
"	*Niotha clathrata* e *Zeuxis scalaris*	Taiwan	1	0	Mean value (maximum value) Digestive gland: 245±98 (330) MU/g in *N. clathrata*; 203±110 (320) MU/g in *Z. scalaris*
Yin et al., 2005; Hwang et al., 2005	*Nassarius glans*	Taiwan	6	2	Mean value (maximum value) Digestive gland: 538±608 (2048) MU/g; Flesh 1167±557 (2992) MU/g. Mean total toxicity of specimens: 5188±1959 MU.
Sui et al., 2001	*Zeuxis samiplicutus*	China	31	0	Digestive gland: 370±118 (532) MU/g; Edible parts: 307±192 (688) MU/g. Mean total toxicity of specimens: 111±45 MU.

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