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# Marine Biotoxins: Origins, Effects, Distribution, Prevention and Treatment

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**Abstract:- A set of marine toxins can be the cause of serious poisoning, the most well-known are amnesic shellfish poisoning (ASP), Diarrhetic shellfish poisoning (DSP), neurotoxic shellfish poisoning (NSP), Paralytic shellfish poisoning (PSP), pufferfish poisoning (PFP), Ciguatera fish poisoning (CFP) and azaspiracid shellfish poisoning (AZP). These marine food intoxications are neither rare nor new, but they are a result of fisheries and the increase of tourism sector. We are witnessing a universalization of problems which was previously endemic. The various forms of poisoning that can occur after the consumption of contaminated marine products, the toxins responsible, its global geographical distribution, and its effects on human health as well as the rest of living beings interacting with the marine sector, prevention and treatment for each intoxication are discussed in this review.**

***Keywords:-*** *Marine Toxin, Poisoning, Seafood, Geographical Distribution, Prevention And Treatment.*

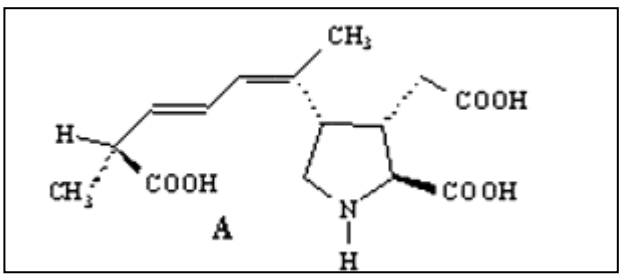
## I. INTRODUCTION

Man is a foreigner in aquatic environments and his lack of knowledge makes him an easy victim of the toxins developed by marine organisms. It is estimated that 60% of the world's population lives along coastal areas and that most of them draw their source of survival from the sea [1]. This deep relationship, which unites the ocean and Man, is primarily due to the high-quality nutritional values provided by marine products and their diversity [2]. But these riches are also involved in several intoxications of marine origin, the responsible of which are microscopic algae. Generally, these phytoplankton are present in small quantities, with no adverse impact on the environment or human health [3]. On the other hand toxicity, settles when the conditions in their environment become favorable for proliferation and/ or aggregation thus forming dense concentrations of cells, this phenomenon is recognized as the concentrated proliferation of harmful algae that can color the waters, and give the '"red tides" [4]. These intoxications manifest in the form of neurological, gastrointestinal and other diseases, introduced either by simple contact with seawater, either by inhalation of airborne substances or by consumption of toxins accumulated throughout the food chain. The four kinds of seafood poisoning are diarrhetic, neurotoxic, amnesic and paralyzing pathologies. The least serious is the one that causes diarrhea, a particular type of dinoflagellates is responsible for the production of the poison, the okadai acid. With regard to neurointoxication at least ten compounds are responsible including brevetoxinstoxique. Amnesia intoxication is caused by the production of domoic acid by algae, diatoms. Paralytic intoxication is potentially the most serious. It is mainly caused by saxitoxin produced by dinoflagellates and cyanobacteria. The main purpose of this literature review is to provide an overview of the intoxications of the most well-known marine origins and to present their origins, modes of action and structures. It also aims to show the global distribution of its toxins and the major prevention and treatment measures in place to prevent and sensitize consumers to the dangers that seafood can cause. However, it must be emphasized that data on marine toxins are changing rapidly and that there are still many unknowns.

## II. THE MAIN MARINE TOXINS AND THEIR POISONING

### *A. Domoic acid:*

Domoic acid (DA) and they isomers are produced by diatoms of the genus Pseudonitzschiaspp [5].It is a family of phycotoxins that leads to amnesic intoxication by seafood (ASP). DA is the bace molecule and there is 10 isomers, but only domoic acid and its analogue epidomoic acid are considered toxic [6] "Fig. 1."



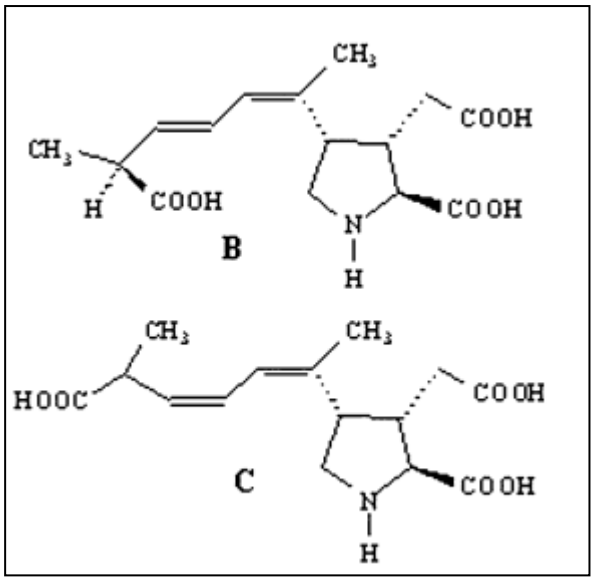



Fig. 1: General structure of domoic acid and they isomers ; A domoic acid; B epi-domoic acid; C isodomoic acid (A. Lo´ pez-Rivera and al. 2005. Improved high-performance liquid chromatographic method for the determination of domoic acid and analogues in shellfish: effect of pH,AnalBioanal Chem., 381: 1540–1545).

AD is recognized being an excitatory molecule of the dicarboxilic amino acid, the latter binds with a strong affinity to the kaïnate (Kd - 5 nM) and α-amino-acidGlutamate receptor 3-hydroxy-5- methyl-4-isoxazoleproprionic (AMPA) (Kd -9nM) [7] [8]. This powerful agonist causes continuous stimulation of the neurons, with an increase in intracellular calcium reaching very toxic levels leading to necrosis of the neuronal cells of the hippocampus at the levels of CA1 and CA3 “Fig. 2,” [9].

DA is particularly recognized for its ability to produce mild to severe neural symptoms in people who have consumed contaminated molluscs, including transient amnesia, dizziness, disorientation and memory loss [10] even in coma, then to death [9], more than gastrointestinal disorders, nausea, vomiting, abdominal cramps and diarrhea [11]. ASP in humans was first reported in 1987 in Prince Edward Island, Canada. During this event, three people died and more than 100 were hospitalized after consuming blue mussels (Mytilusedulis) that had high levels of DA [9].

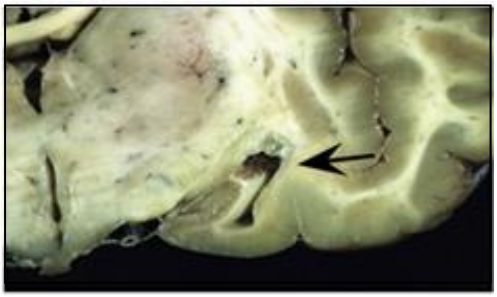
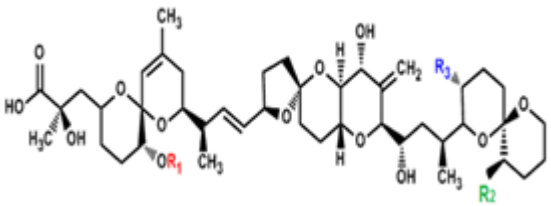


Fig. 2: Photo taken for the seahorse of a California sea lion (Zalophuscalifornianus) from 100 other adults who consumed Nordic anchovies (Engraulismordax) contaminated with domoic acid from a harmful algae proliferation of diatom Pseudo-nitzchiaaustralis. The animal was euthanized for several months. General necropsy revealed atrophy of the hippocampus and a relative enlargement of the lower horn of the lateral ventricle (arrow). Atrophy can occur following convulsions induced by domoic acid. (Solter P.F and R. Beasley Val. 2013. Chapter 38; Photo taken by Paul Silvagni Philip).

*B. Okadaic acid:*

Okadai acid (OA) was initially isolated from sea sponges belonging to the genus Halichondria spp. including H. okadai [4] where its name comes from and by dinoflagellates such as the Dinophysis genus, D. Fortti [8] [9] and the genus Prorocentrumspp [10] [11] . OA is a lipophilic polyether compound, belonging to a class of seven other dinophysistoxin (DTXs) congeners [9] . The latter were isolated from the digestive glands of crustaceans and identified as toxins responsible for diarrhetic shellfish poisoning (DSP) [8] [11]. OA, DTX1,DTX2 and a number of fatty acid esters derived from these three parental toxins (known generically as DTX3) “Fig. 3,”are structurally similar and act according to a similar mechanism of action, these are potent inhibitors of serine/ threonine, protein phosphatase type 1 (PP1) and type 2A (PP2A) [4] [12], this inhibitory activity leads to increased phosphorylation of myosin and other phosphorylated proteins, resulting in an influx of calcium, constant production of AMPC or prostaglandins ending in the continuous secretion of fluid in the cells of the intestine [9]. It is then, that consumption of contaminated molluscs at high levels of toxins will cause gastrointestinal symptoms to appear quickly 3 hours after ingestion [13], such as, diarrhea, abdominal cramps, nausea and vomiting but which disappear in 2-3 days [4] [14] , and in the most severe cases, we notice dizziness, seizures, hallucinations and short-term memory loss [10]. The DSP is suspected to be produced the very first time in 1961 in the Netherlands but the reasons remained unknown, until the 1970s following the epidemics produced in Japan, the toxins involved were identified [9].



Okadaic acid (AO) : R1=H ; R2=CH3 ; R3=H
Dinophysistoxines 1 (DTX1) : R1=H ; R2=CH3 ; R3= CH3
Dinophysistoxines 2 (DTX2) : R1=H ; R2=H; R3= CH3
Dinophysistoxines 3 (DTX3) : R1=Acyl ;R2/R3= CH3/H

Fig. 3: The structures of okadaic acid (OA), dinophysistoxin 1 (DTX1), dinophysistoxin 2 (DTX2) and dinophysistoxin 3 (DTX3). (Figure reproduced from the manual by Lampel K A., S. Al-Khaldi and MS. Cahill MS. 2012. Bad Bug Book: Foodborne Pathogenic Microorganisms and Natural Toxins Handbook Okadaic Acid and Dinophysis Toxins).

*C. Brevetoxin:*

Brevetoxins (BTX) are a group of more than ten cyclic, natural polyether neurotoxins produced by marine dinoflagellates of the genus Karenia spp., of which the species, K. mikimotoi, K. brevisulcata, K. selliformis and K. papilionacea [15] and the most recognized and best studied is K. brevis, formerly known as Gymnodinium breve and Ptychodiscus brevis [10] [15] . Recent studies have indicated that BTX can also be produced by Chatonellaspp [16]. Depending on their skeletal structure, BTXs are divided into two types of fat-soluble toxins: Type 1 (neurotoxins) which are the (brevetoxin B), grouping the (BTX- 2,3,5,6,8,9) and type 2 (hemolytics) which are (brevetoxin A) containing the (BTX-1,7,10) "Fig. 4,"however the chemical structure of the BTX4 is not yet discovered [8] [17] . BTX are shown to be responsible for neurotoxic shellfish poisoning (NSP), but at unequal levels of toxicity, of which BTX1 and BTX2 are the most potent [15]. These cyclic polyether structures bind with high affinity (Kd 1 -50 nM) [8] to the orphaned S5 receptors located on the α subunit of the voltagedependent sodium channels (Cnavd), acting on the central and peripheral nervous system [4] [10]. The specific binding of brevetoxins to synaptosomes was first demonstrated by Poli and his colleagues in 1986, it leads to an inappropriate opening of Cnavd to a normal value of the resting potential, and allows the persistent activation of the sodium channels, while slowing and delaying their inactivation [8] [11] . In this effect, a massive and uncontrollable entry of NA+ ions results, leading to spontaneous depolarization of nerve and muscle cells [15] . This results in a continuous release of the neurotransmitters by the neurons thus leaving a state of permanent subconductance [18]. NSP in humans may be involved through two routes of exposure. Either by eating the contaminated molluscs which leads to symptoms such as nausea, abdominal cramps, weakness and difficulty of movement, paralysis, convulsions and in the most severe cases coma and death [19] [20] . Either by inhalation, during the red tides "Fig. 5," under the action of the surf, the cells of the G.breve, lyse and break in the water while releasing airborne toxins, which causes irritation of the respiratory tract and vertigo, tunnel vision and rashes [19] [21] . Walker was the first to register an NSP in 1880 on the west coast of Florida [22].

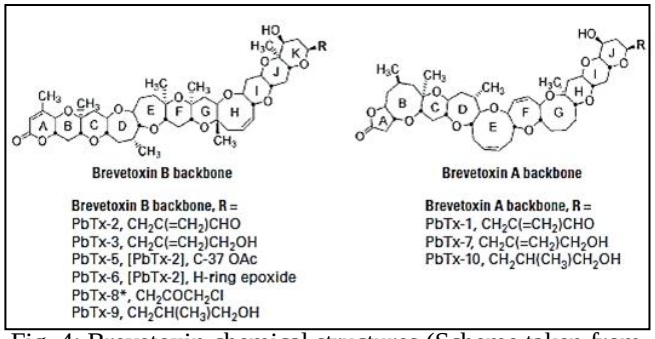


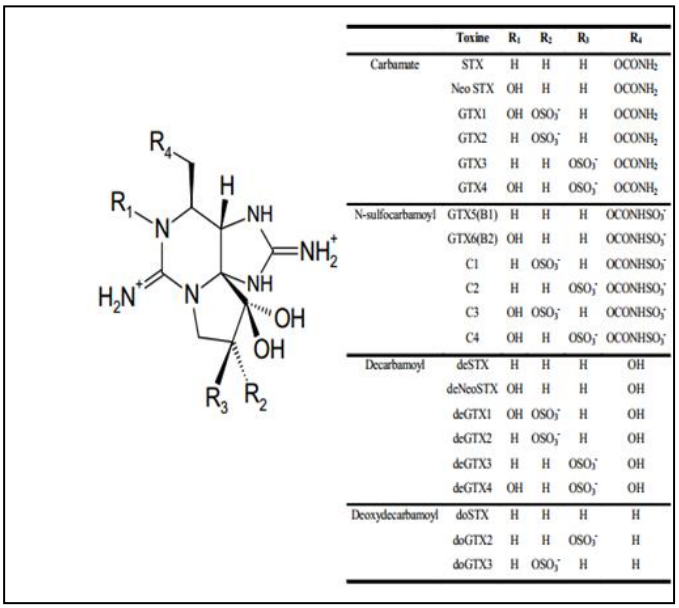

Fig. 4: Brevetoxin chemical structures (Scheme taken from Andrew D. Turner, Cowan Higgins, Keith Davidson, Andrea Veszelovszki, Daniel Payne, James Hungerford and Wendy Higman, 2005: Natural and Derivative Brevetoxins: Historical Background, Multiplicity, and Effect. Environmental HealthPerspectives, VOLUME 113 | NUMBER 5 p.621-625).

Fig. 5: Photo of a red tide off La Jolla, California. (Removed from Chand, P. 2009. Seafood Neurotoxins I: Shellfish Poisoning and the Nervous System. Clinical Neurotoxicology, 441–447, page 442).

*D. Saxitoxin:*

Saxitoxins (STX) are produced by several genera of dinoflagellates such as Alexandrium spp., Gymnodinium spp. and Pyrodinium spp., Although their production has also been observed by many genera of cyanobacteria, including Anabaena spp. , Aphanizomenon spp. , Cylindrospermopsis spp., Lyngbya spp., and Planktothrixspp[4] [23]. The name saxitoxin is derived from the American clam, Saxidomusgiganticus, from which the toxin was first isolated in 1957 [4]. STX are alkaloids, molecular formula C10H17N7O4 (299 DA), composed of a 3.4-propinoperhydropuric tricyclic system, belonging to the large family of natural marine products containing guanidinium the family can be divided into four categories "Fig. 5." Since its initial discovery, 57 naturally occurring STX analogues have been identified in a number of organisms. They are collectively responsible for Paralytic shellfish poisoning (PSP) in humans [24] [25]. These toxins, synthesized by the aforementioned gonyaulax species, accumulate in certain filter molluscs such as mussels, oysters, clams and scallops. Although bivalves are considered as traditional vectors and bio-indicators of paralytic toxins, non-traditional vector declarations are increasingly recognized, the latter being marine gastropods, crustaceans, echinoderms, tunicates and ascidians, which can accumulate toxic levels of SXT. PSP, occurs when STX binds reversibly and with high affinity (Kd - 2 nM), at Cnavd site 1, blocking its conductivity, while stopping membrane permeability to Na+ ions [8], resulting in smooth vascular muscle relaxation, a decrease in the potential for action of the heart muscle and prevents the spread to skeletal muscles [26].However, sensory nerves are shown to be more susceptible to sodium channel blockage by STX than motor nerves, and sensory abnormalities usually precede paresis and paralysis [4]. Although the exact cause of the PSP was identified in 1927 off the coast of central California, by Sommer the poisoning by SXT can be traced in medical literature for centuries, the first report was dated 1798 [27]. PSP is accompanied by a set of symptoms that usually begin within 5 to 60 minutes after consuming toxic molluscs [28],

the adverse effects can be classified into three levels ofintoxication depending on their severity on health and life, a benign stage, presented by tingling or numbness around the lips that spreads to the neck and face. In a progressive state, stinging sensation of the fingertips, headache, sometimes increased salivation, vomiting of nausea and diarrhea. A severe stage, expressed by a paresthesia of the face, lips and tongue, then of the arms and legs, incoherence of speech, affected people may complain of dizziness or a floating sensation. And in a very extreme stage, usually associated with ingestion of high doses of toxin, it induces ataxia, dysphagia and changes in mental status with respiratory failure due to paralysis of the diaphragm and chest wall muscles which may eventually lead to death without respiratory assistance [9] [11] [29].




| | Toxine | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|---|
| Carbamate | STX | H | H | H | $OCONH_2$ |
| | Neo STX | OH | H | H | $OCONH_2$ |
| | GTX1 | OH | $OSO_3^-$ | H | $OCONH_2$ |
| | GTX2 | H | $OSO_3^-$ | H | $OCONH_2$ |
| | GTX3 | H | H | $OSO_3^-$ | $OCONH_2$ |
| | GTX4 | OH | H | $OSO_3^-$ | $OCONH_2$ |
| N-sulfocarbamoyl | GTX5(B1) | H | H | H | $OCONHSO_3^-$ |
| | GTX6(B2) | OH | H | H | $OCONHSO_3^-$ |
| | C1 | H | $OSO_3^-$ | H | $OCONHSO_3^-$ |
| | C2 | H | H | $OSO_3^-$ | $OCONHSO_3^-$ |
| | C3 | OH | $OSO_3^-$ | H | $OCONHSO_3^-$ |
| | C4 | OH | H | $OSO_3^-$ | $OCONHSO_3^-$ |
| Decarbamoyl | deSTX | H | H | H | OH |
| | deNeoSTX | OH | H | H | OH |
| | deGTX1 | OH | $OSO_3^-$ | H | OH |
| | deGTX2 | H | $OSO_3^-$ | H | OH |
| | deGTX3 | H | H | $OSO_3^-$ | OH |
| | deGTX4 | OH | H | $OSO_3^-$ | OH |
| Deoxydecarbamoyl | doSTX | H | H | H | H |
| | doGTX2 | H | H | $OSO_3^-$ | H |
| | doGTX3 | H | $OSO_3^-$ | H | H |

Fig. 6: structure of the Saxitoxins. (Van Dolah, F. M. In Seafood Toxicology: Pharmacology, Physiology and Detection Botana, L. M., Ed.; Marcel Dekker: New York, 2000, p 19-43).

*E. Tetrodotoxin:*

Tetrodotoxin (TTX) is a powerful neurotoxin first discovered in 1909 by DrYoshizumiTahara, which he isolated from the ovaries of the globe fish (balloonfish) [30]. This toxin returns to the tetraodontid family, from which derived the name tetrodotoxin [31]. However, prior to 1964, TTX was thought to be present only in glob fish but was later detected in various marine [32] [33] [34] and terrestrial animals “Fig. 7” [35]. More recently, it has been shown that the origin of this toxin are intestinal marine bacteria, limited to 20 species of Pseudoalteromonas spp., Pseudomonas spp. and Vibrio spp., some of which are known as symbiotes, passed along the entire food chain to puffer fish [36]. Nevertheless, the source of the TTX is still a controversial debate between the researchers, on the test that the TTX is of symbiotic, endogenous or exogenous origin [37]. In the mid-1960s, Tsuda Woodward and Goto revealed that TTX has a very unusual structure “Fig. 8,” a highly oxygenated carbon skeleton, some of which is composed of 2.4 dioxaadamantane containing five hydroxyl groups connected to cyclic guanidine [38] [39]. Since then, 13 TTX analogues have been isolated. TTX is a potent and lethal neurotoxin that selectively inhibits the mechanism of activation of nerve impulse; it has the same effect as STX but has proven stronger [40]. These guanidinium groups, comprising a central carbon atom and three nitrogen atoms with a positive load at physiological pH, confer the binding capacity to Cnavd site 1 blocking the current of Na+ ions entering the excitable cells, mainly in muscles and nerves, without affecting the permeability of K+ ions [41]. This action causes intoxication known as pufferfish poisoning (PFP), which leads to extensive paralysis and in the most extreme cases, to death. Poisoning with TTX usually begins 30 min after ingestion of the toxin at 6 hours after consuming contaminated fish, passing through four progressive stages. First, oral paresthesia with or without gastrointestinal symptoms. Second, paresthesia in other areas and motor paralysis. Third, muscular incoordination, aphonia, dysphagia, respiratory distress, cyanosis and hypotension. Finally, respiratory paralysis and hypotension and then death [42]. The mortality rate due to TTX poisoning depends, among other things, on access to critical care facilities. Patients, who have not died within 24 hours, usually recover. As with PFP, the symptoms of TTX poisoning are completely resolved in 1 to 2 days [43]. On the other hand, the fact that TTX can also block certain Cnavd, at the level of sensory nerves [44], it has become an important chemical in neuroscience, used in anesthesia and analgesia or for cancer-related pain [45].

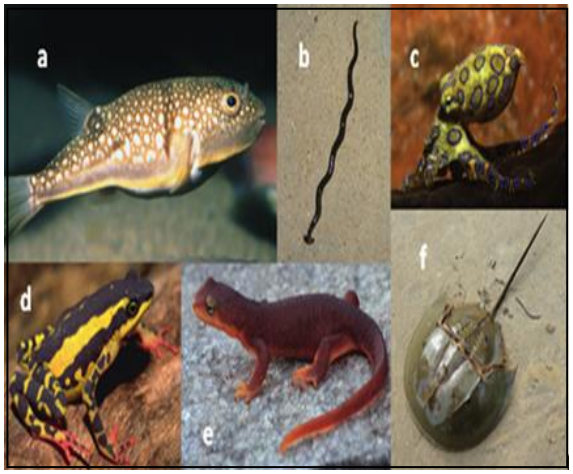



Fig. 7 (a): Butterflyfish (Takifugupoecilonotus) from the Pacific Northwest; (b): A hammerhead "slug" (Bipaliumkewense) from Asia, Europe and North America; (c): The blue ringed octopus (Hapalochlaenalunulata) from Australia; (d): the harlequin frog of the coast (Atelopus tricolor) of the Amazonian slope; (e) The rough-skinned newt (Taricha granulosa) from western North America; (f): The crabeater (Tachypleusgigas) from the Indian and Pacific oceans. (Photos Credits: KeokiStender, Ajaykuyiloor (Wikimedia), Gustavo Maqueda, JörnKöhler, William Leonard, Shubham Chatterjee (Wikimedia).

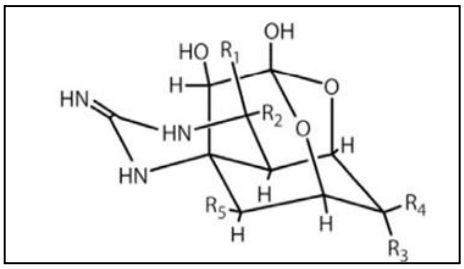


Fig. 8: The basic structure of the group composed of tetrodotoxin and its congeners (after: Durán-Riveroll L.M. and A. D. Cembella. 2017).

*F. Ciguatoxin:*

Ciguatoxins (CTX) are phycotoxins synthesized from dinoflagellates of the genus Gambierdiscus spp., amicroalga associated with coral reefs in the tropical Pacific Ocean [46], the Indian Ocean [47]and the Caribbean [48] . However, it has been shown that other species are capable of producing them, namely, the genus Prorocentrum ssp., Ostreopsis spp., Thecadinuim spp. and the two species, Cooliamonotis and Amprodinuimcarterae [49][50]. Phycotoxins of type CTX are lipophilic neurotoxins, polyethers of molecular weight of 1110 Da, composed of 10 to 14 cycles transfused by ether bonds. Depending on the region of origin, the CTX are divided into three families "Fig. 9:" The P-Ctxs (Pacific Ocean) [51], the C-CTX (Caribbean) and the I-CTX (Indian Ocean). The CTX accumulate through the food chain, from fish consuming algae, to carnivorous fish, before occurring to humans [10]. There are more than 400 species considered to carry these toxins, including groupers, red snappers, see bass, barracuda emperor fish, Spanish mackerel, amberjacks [52]. Ctxs are responsible for Ciguatera fish poisoning (CFP), another seafood intoxication, [10] [42]. They have the same mechanism of action as the brevetoxins, while binding to the S5 site on the Cnavd (Kd - 0.04-4 nM) but even more powerful [53]. The bond created between the toxin and the canal acts directly on neuromuscular junctions, sensory neuronal membranes and other excitable cells, inducing depolarization by selective opening of the sodium channels voltage dependent on the normal resting potential [4] [54]. CFP appears within 10 to 30 minutes of ingestion and is characterized by varying combinations of gastrointestinal, neurological and cardiovascular symptoms. Often digestive symptoms disappear in 1-2 days, cardiovascular in 2-5 days, and neurosensory in 2-3 weeks [52]. Death may occur as a result of direct cardiovascular depression, hypovolemic shock or respiratory paralysis [55]. However, the typical symptom of this poisoning is temperature inversion, where patients interpret cold as a burn. In addition, nerve biopsies from human patients showed swelling of Schwann cells with axon compression and vesicular degeneration of myelin [4]. CFP, can be transmitted through sexual intercourse, it can also harm the health of the fetus in pregnant womenn sometimes causing an abortion [56]. The first intoxication case appeared in 1550 in the Caribbean after people consumed contaminated reef fish [57].

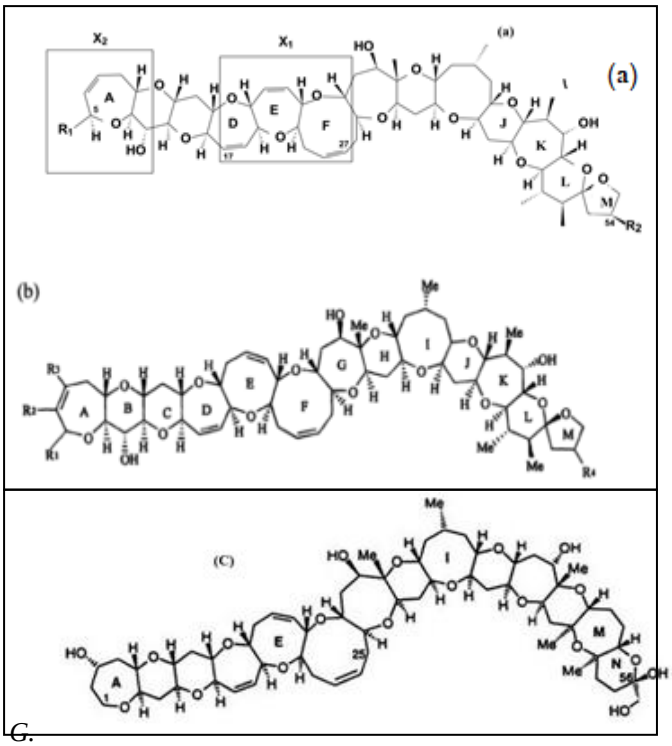


Fig. 9: The basic structures of CTX: (a) The family of P-CTX type 1; (b) The type 2 P-CTX family; (c) The C-CTX family; I-CTX are not yet identified (from books of Ménez A., 2002; Caillaud A., et al., 2010.

*G. Azaspiracid:*

Azaspiracids (AZA) are polyether, highly oxygenated lipophilic toxin with an unusual structure [58], formed by a cyclic amine (or aza group), a unique tri-spiro assembly and a carboxylic acid group, hence the name AZA- SPIR-ACID, [59]"Fig. 10," the structure of the first azasparacid, AZA1, (molecular weight 841.5 Da) was reported in 1998 after isolation from Irish blue mussels (Mytilusedulis) and modified in 2004. For years, AZAs were thought to be produced by dinoflagellate Protoperidiniumcrassipes, but it has recently been discovered that its origin actually comes from other genera of dinoflagellates, including Azadiniumspp [60], and Amphidomaspp, [61]. This can be explained, that P. crassipes feeds on A. spinosum and thus accumulates the toxin. In addition [4] , AZAs are found in filter-feeding molluscs such as blue mussels (M. edulis) from Ireland, oysters (C. gigas and Ostreaedulis), Chilean mussels (Mytiluschilensis), razor shell (Ensissiliqua) and scallops (Pectenmaximus and Argopectenpurpuratus), as well as in crustaceans such as crabs (C. pagurus) [62]. Due to extensive metabolism in molluscs and crustaceans, more than 40 AZA structures have been identified "Fig. 11" [63]. In contrast, AZA1, AZA2 and AZA3 are the most toxic [64]. In 1995, a group of eight Dutch consumers experienced food poisoning after consuming shellfish harvested on the Irish coast [65]. The symptoms described appeared to be consistent with those associated with DSP. However, in the analysis of the samples, small quantities of the OA were found [66]. Later, AZAs are recognized as a unique group of algal toxins causing azaspiracid shellfish poisoning (AZP). Several articles have been published on

azaspiracids but do not incorporate their mode of action in humans, which remains unknown until now. In this case, studies have worked on their toxicological effects on animals. For example i.p. injection in mice with extracts of contaminated shells causes the appearance of neurological symptoms, namely respiratory difficulties, spasms and progressive paralysis [67] followed by death within 20 to 90 minutes after injection[68] .Oral exposures of AZA1 led mice to changes in the gastrointestinal tract, liver and lymphoid organs, lungs [69] the pancreas, thymus, spleen, and was also the cause of tumours [4]. Other in vitro studies have shown that AZA1, 2 and 3 were weak and moderate blockers of K+. Roman and his team in 2002, estimate that AZAs primarily AZA1 cause an increase of [Ca2+] intracellular and the AMPC in lymphocyte cells as well as alteration of cytoskeletal actin F in Jurkat cells [70]. AZP is primarily manifested by severe gastrointestinal symptoms, including diarrhea, nausea, vomiting and stomach cramps [4].

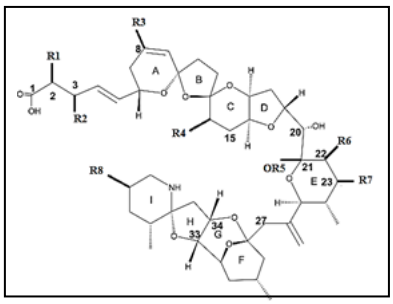
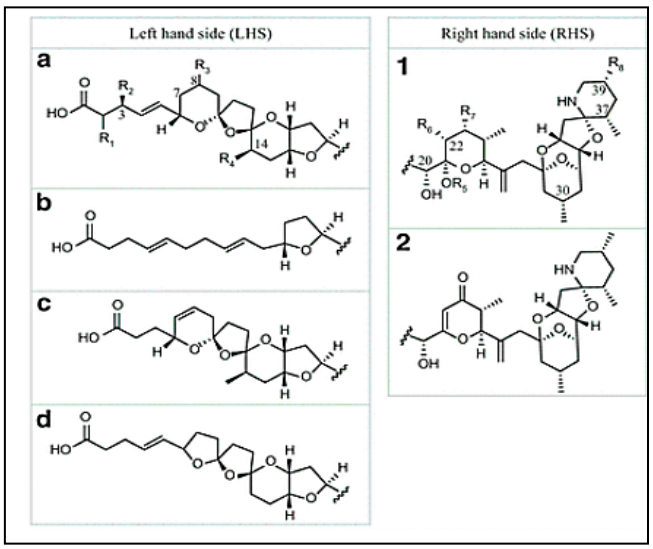


Fig. 10: The basic chemical structures of azaspiracids (Modified figure, drawn by Nicolaou KC, Frederick MO, Petrovic G., Cole KP, Loizidou EZ 2006. Total synthesis and confirmation of the revised structures of Azaspiracid-2 and Azaspiracid-3. Angew Chem. Int. Ed. Engl. 45, 2609-2615).




| | Type[b] | $R_1$ | 7,8 | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | $R_8$ | Status |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AZA1 | a1 | H | Δ | H | H | $CH_3$ | H | $CH_3$ | H | $CH_3$ | phycotoxin |
| *37-*epi*-AZA1 | a1 | H | Δ | H | H | $CH_3$ | H | $CH_3$ | H | $CH_3$ | artefact |
| AZA2 | a1 | H | Δ | H | $CH_3$ | $CH_3$ | H | $CH_3$ | H | $CH_3$ | phycotoxin |
| AZA3 | a1 | H | Δ | H | H | $CH_3$ | H | H | H | $CH_3$ | metabolite |
| AZA4 | a1 | H | Δ | OH | H | $CH_3$ | H | H | H | $CH_3$ | metabolite |
| AZA5 | a1 | H | Δ | H | H | $CH_3$ | H | H | OH | $CH_3$ | metabolite |
| AZA6 | a1 | H | Δ | H | $CH_3$ | $CH_3$ | H | H | H | $CH_3$ | metabolite |
| AZA7 | a1 | H | Δ | OH | H | $CH_3$ | H | $CH_3$ | H | $CH_3$ | metabolite |
| AZA8 | a1 | H | Δ | H | H | $CH_3$ | H | $CH_3$ | OH | $CH_3$ | metabolite |
| AZA9 | a1 | H | Δ | OH | $CH_3$ | $CH_3$ | H | H | H | $CH_3$ | metabolite |
| AZA10 | a1 | H | Δ | H | $CH_3$ | $CH_3$ | H | H | OH | $CH_3$ | metabolite |
| AZA11 | a1 | H | Δ | OH | $CH_3$ | $CH_3$ | H | $CH_3$ | H | $CH_3$ | metabolite |
| AZA12 | a1 | H | Δ | H | $CH_3$ | $CH_3$ | H | $CH_3$ | OH | $CH_3$ | metabolite |
| AZA13 | a1 | H | Δ | OH | H | $CH_3$ | H | H | OH | $CH_3$ | metabolite |
| AZA14 | a1 | H | Δ | OH | H | $CH_3$ | H | $CH_3$ | OH | $CH_3$ | metabolite |
| AZA15 | a1 | H | Δ | OH | $CH_3$ | $CH_3$ | H | H | OH | $CH_3$ | metabolite |
| AZA16 | a1 | H | Δ | OH | $CH_3$ | $CH_3$ | H | $CH_3$ | OH | $CH_3$ | metabolite |
| AZA17 | a1 | H | Δ | H | H | $CH_3$ | H | COOH | H | $CH_3$ | metabolite |
| AZA19 | a1 | H | Δ | H | $CH_3$ | $CH_3$ | H | COOH | H | $CH_3$ | metabolite |
| AZA21 | a1 | H | Δ | OH | H | $CH_3$ | H | COOH | H | $CH_3$ | metabolite |
| AZA23 | a1 | H | Δ | OH | $CH_3$ | $CH_3$ | H | COOH | H | $CH_3$ | metabolite |
| AZA26 | a2 | H | Δ | H | H | $CH_3$ | - | - | - | - | metabolite |
| AZA29 | a1 | H | Δ | H | H | $CH_3$ | $CH_3$ | H | H | $CH_3$ | artefact |
| AZA30 | a1 | H | Δ | H | H | $CH_3$ | $CH_3$ | $CH_3$ | H | $CH_3$ | artefact |
| AZA32 | a1 | H | Δ | H | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | H | $CH_3$ | artefact |
| AZA33 | b1 | H | Δ | - | - | $CH_3$ | H | $CH_3$ | H | $CH_3$ | phycotoxin |
| AZA34 | c1 | H | Δ | - | - | $CH_3$ | H | $CH_3$ | H | $CH_3$ | phycotoxin |
| AZA36 | a1 | H | Δ | OH | $CH_3$ | $CH_3$ | H | $CH_3$ | H | H | phycotoxin |
| AZA37 | a1 | H | - | OH | H | $CH_3$ | H | $CH_3$ | H | H | phycotoxin |
| AZA38 | a1 | H | - | $CH_3$ | H | H | H | $CH_3$ | H | H | phycotoxin |
| AZA39 | d1 | $CH_3$ | - | H | - | H | H | $CH_3$ | H | H | phycotoxin |
| AZA40 | a1 | H | Δ | H | $CH_3$ | $CH_3$ | H | $CH_3$ | H | H | phycotoxin |
| *AZA41 | a1 | H | Δ | H | $CH_3$ | $CH_3$ | H | $CH_3$ | H | $CH_3$ | phycotoxin |

Fig. 11: Structural variants of AZAs (Reproduced from Hess, P., M. J. Twiner, J. Kilcoyne and S. Sosa. 2015. Azaspiracid Toxins: Toxicological Profile. Marine and Freshwater Toxins, 1–19).

## III. THE GEOGRAPHICAL DISTRIBUTION OF MARINE BIOTOXINS

These last years have seen the extension of marine phycotoxins all along the litoral zones of the terrestrial globe, following an increase in the number of toxic algal blooms “Fig. 12.”

### *I. The Domoic acid*

The species responsible for ASP have been detected at geographic sites such as Canada, New Zealand, the Californian coast, and also at the level of several European countries, in particular in Scotland, Denmark, Spain, Portugal, Italy and Korea [71] [72] [73] . France is not immune to this poisoning, traces of DA have been detected in some mussels but at concentrations of (0.5 µg AD/g flesh) [74] that do not exceed the regulatory threshold prescribed by the European Union (EU) (20 µg AD/g shell meat) [75].


Fig. 12: Global distribution of different marine toxins.

*J. Okadaic acid :*

The DSP is the most widespread, it can be observed almost every year in France (Bay of Seine, on the coastal region of Cotentin, the Arcachon basin, the Mediterranean lagoons of Languedoc-Roussillon and the Diana Corsican ponds), in Italy, in the north-eastwestern Spain [76] , Portugal (Azores and Madeira) [77] and Canada. Moreover, OA is much less widespread in the coastal regions of Brittany [78] [79]. The OA was also found in Japanese waters and along the Chinese coast [80]. In Africa, this toxin was found in coastal areas of Morocco [81], the example of the species of Dinophysisfortii that was detected in the Moroccan Atlantic coast by Akallal in 2002 but in small quantities [82]. The distribution of the species that produce the toxin extends from temperate waters to warm areas containing coral reefs. The periods of toxicity vary from region to region and are generally related to periods of species development [10] [79]. The limit value currently implemented in EU legislation is 0.16 mg/kg shell meat [83].

*K. Brevetoxin:*

Brevetoxin is a potent neurotoxin whose diseases are mostly reported in coastal areas of Florida and in the Caribbean [84] [85].Although some blooms of Karenia species have been observed recently in Europe [86], but so far, NSP, is still limited to the United States (Florida), the Gulf of Mexico, New Zealand and also South Africa [87], (only massive mortalities of fish, birds and marine mammals were recorded [88], but no human mortality was reported [89] . There are currently no regulatory limits by the European Food Safety Authority (EFSA) or the European Union for BTX group toxins. Nevertheless, the European Commission regarding marine biotoxins has set a regulatory limit of 800µg of BTX/kg of seafood flesh/fish, this value is set by the FDA (Food and Drug Administration) of the United States [90].

*L. Saxitoxin:*

The main producers of toxins responsible for PSP are known to occur along the northern and southern hemispheres [91], both genera, Gymnodinium spp. and Pyrodinium spp. were found in the Mediterranean Sea [92]. STX exist seasonally in North America, both on the east coast (from Newfoundland to Massachusetts) and on the west coast (from Alaska to California). However, prior to the 1970s, STX was endemic only in North America, Europe and Japan, and PSP epidemics are also documented in South America, Australia, Southeast Asia and the Indo-Pacific. (New Guinea Papua, Philippines and Malaysia). A study by Anderson and his colleagues in 1996, estimated that in China, which is recognized by its red tides, a total of 40 to 50 incidents of PSP is reached per year [8] [93] , other epidemics were reported in the United States and Canada [10], and on the Moroccan coast in particular, Casablanca, El Jadida, SidiBouzid, Mrizika, Oualidia [94] and Souss Massa (Agadir) [95] . This expansion of toxin was explained by climate change more than the introduction of dinoflagellates by sea transport [8]. To date, STX-producing species are distributed around the world [96] [97] (Shumway 1990; 1995), which is why a regulatory limit is set by the EU (0.8 mg/kg shell meat) to minimize the risk of poisoning [98].

The Tetrodotoxin: the PFP is very common in Japan, Taiwan, Bangladesh and Southeast Asia [99][100]. But over the past decade, TTX has been found in European countries [101], cases reported in Spain for example [102]. A number of researchers explained the new occurrence of TTX in European regions by the migration of Lessepsian. Indeed, in 1869 the opening of the Suez Canal led to the migration of many species from the Red Sea to the eastern Mediterranean [99][103]. Or by ballast water, which can also cause the transfer of organisms containing TTX from Asian waters to European waters [104]. However, over the past 20 years, the spread of marine mucilage in the Mediterranean has been observed due to the warming of the sea surface [105]. The TTX was also found in globe fish collected from the Baja coast of the California Peninsula, Mexico [106]. Other countries have recognized cases of poisoning by the TTX, namely Morocco (case of a family occurring in Morocco, by ingestion of canned fish eggs) [107].

*M. Ciguatoxin:*

CFP is specific to the tropical island regions where we find coral reefs of the three great oceans: Pacific Ocean (French Polynesia, New Caledonia, Australia, Vanuatu, Hawaii, Japan), Atlantic Ocean and Indian Ocean. It is also in Florida [108]. This intoxication is very old, exists for centuries [109], it began in the Caribbean at the beginning of the 16 centuries, in the Indian Ocean on Mauritius from 1601 and in the New Hebrides in 1606 [108]. In 2003, the genus Gambierdiscus spp. was highlighted in the Mediterranean on the Cretan coast, and in the Atlantic and the Canary [110]. Fish containing ciguatoxin compounds have also been found in Israel [111]. Within the EU, only countries with outermost regions, located in the tropics and very far from the European continent, exposed to ciguatera, in particular, Portugal (Azores and Madeira), France (Guadeloupe, Saint Martin, Guyana, Martinique and Réunion. Mayotte) and Spain (Canary Islands). On the other hand, at the beginning of 2012, several episodes of ciguatera were reported in Guadeloupe. To date, the EU has not indicated a regulatory threshold or specified feasible analytical methods for CTXs [112]. Nevertheless, the European Food Safety Agency has specified that a dose of 0.01 µg P-CTX1 equivalent/kg shell meat would not cause adverse effects in humans [113].

*N. Azaspiracid:*

After the first documented episodes of AZP in 1995 in the Netherlands, new cases were announced in Ireland and other countries after the consumption of exported Irish mussels. Since then, AZAs have been detected in Europe (UK, Norway, France, Portugal), North Africa (Morocco), South America (Chile) between 1995 and 2007[67] , and more recently in the United States and Japan [114] . From a seasonal perspective, it appears that AZA contamination of shellfish above the EU regulatory limit (0.16 mg/kg shell meat) was detected between mid-summer and mid-winter,

from western waters to the west, now arriving at the extreme of Morocco (July, ~ 0.9 µg/g) [67].

## IV. PREVENTIONS AND TREATMENT TAKEN AGAINST MARINE TOXINS:

Globally, phycotoxins are responsible for over 60,000 intoxication incidents per year, with an overall mortality rate of 1.5%. As well as their effects on human health, marine toxins are responsible for the massive mortality of fish, molluscs and crustaceans and the episodic mortality of marine mammals, birds and other animals dependent on the marine food web[8].

*O. The ASP:*

No cases of human disease associated with the consumption of DA have been reported except in North America. However, data on ASP cases are limited, with the exception of one outbreak in Canada in 1987, including 150 reported cases, 19 hospitalizations, and 4 deaths following consumption of contaminated mussels [115]. The DA also has a toxic effect on marine wildlife, many cases of poisoning have been described in birds and marine mammals. Toxic blooms of diatoms that produce DA pose a permanent threat to human health and the safety of marine products [116]. This is why the DA has followed up on many effective research and monitoring programs in several countries to detect it in shellfish. Similarly, Canada has played a key role in developing measures to limit the risk of exposure of DA to consumers. All of this has resulted in a massive reduction of toxic shellfish entering the market, more than globally, some seafood production sites are frequently closed due to the presence of high levels of these toxins [117] [118] [119]. On the other hand, no antidote is found for this type of intoxication except for palliative treatments [10]. In addition, studies suggest that benzodiazepines can stop some neurological effects of DA such as hippocampal activity and control seizures. In addition, activated carbon can also be used to remove all contaminated and undigested food [120].

*P. The DSP:*

More than 256 cases were reported in China [121], an epidemic focus of DSP, describing three intoxicated people in Washington State [123]. In France, 11 epidemics containing 45 people, intoxicated by OA in 2009 [124]. In 2010, 300 people in northern Italy were poisoned by mussels contaminated with OA [125]. However, the OA mortality rate remains at 0 % [10].

Therefore, the only possible approach currently available to eliminate OA from shellfish is natural detoxification, which involves maintaining these vectors and in the sea for several weeks after the end of the toxic episode [126]. The limit of this treatment and that the natural process of detoxification is slow and depends on the metabolic activity of molluscs, which is usually inhibited by several environmental conditions such as low temperatures [127]. In contrast, after intoxication, patients are retained for symptomatic and adjunct treatment, complete recovery is usually achieved within 3 days [4] [128].

*Q. The PSP:*

Worldwide, nearly 2,000 cases of human poisonings are reported per year, with a mortality rate of 15%, in addition to human intoxication, PSP was involved in the deaths of birds and humpback whales [8]. No antidote or vaccine is prescribed by this kind of intoxication, only palliative treatments, which may consist of gastric washing, and taking activated charcoal that helps eliminate toxins. In more severe cases, artificial respiration and hemodialysis are strongly recommended [129] [130]. In order to combat this deadly poisoning, several countries have implemented programs to monitor and prevent saxitoxin. In cases where the level of the toxin exceeds the regulatory threshold, beaches are prohibited at harvest and shellfish are not permitted for retail sale. In addition, awareness-raising programmes have been set up by governments directed to citizens to take their guard [131].

*R. The CFP:*

Ciguatera poisoning is the most prevalent foodborne disease in the world, with 50,000 to 500,000 incidences per year [132] [133] [134], and despite this high rate, the mortality rate remains very rare with deaths estimated at <0.1% [135]. The export of fish from tropical and subtropical regions, as well as the popularity of these regions for tourism, make this intoxication a global health problem [4]. For example, the health authorities of the countries to which the CTXs belong recommend avoiding the consumption of certain carnivorous fish and removing the head and the food from the reef fish. More generally, they prohibit the consumption of fish whose body weight exceeds 1.5kg [136]. As for the other toxins, the countries endemic to the CFP, monitor in permanaces and ensure the education and awareness of consumers and professionals [131]. On the other hand, no antidote is available. Treatment remains symptomatic with introduction of mannitol; the most effective remedy that leads to a regression of symptoms [4] [137] , In addition, the local traditional medicine is not to be excluded because it has averé effective especially in Polynesia [138] [139] [140].

*S. The PFP:*

The incidence of tetrodotoxin poisoning is very rare, but it is higher in countries where globe fish are regularly eaten, such as Japan, Taiwan and some Southeast Asian countries, for example in Japan, Over a 78-year period from 1886 to 1963, there were 6,386 cases of tetrodotoxin poisoning, with a mortality of about 59% [133]. The increased awareness of fugu intoxication and the strict regulation and training of cooks have significantly reduced the number of cases and reduced mortality in recent years and all over the world. It is now essential that all cooks nowadays and restaurants that handle fish known to be carriers of toxin (fugu) must have a license to cook it as its delicacy to remove the gonads and the viscera are crushed [133]. There is currently no antidote for TTX. Therefore, a

palliative treatment introducing assisted ventilation and atropine infusions to combat hypotension and bradycardia [10] [141].

*T. The NSP:*

So far there are no reported cases of mortality in humans from neurological intoxication. In contrast, 34 manatees and 107 bottlenose dolphins died in Florida between 2002 and 2004 [4] [142]. Since Brevetoxin causes poisoning not only by ingestion of contaminated shellfish but also by aerosol inhalation or by sexual and transplacentaltransmition. It is very clear that regulations must be put in place to eliminate the spread of this marine poisoning. For this purpose, the concentrations of brevetoxin in commercial molluscs and crustaceans are controlled by government surveillance, carried out using biological assay procedures in mice (enzyme-linked immunoassay and radioimmunological assay). The presence of K. brevis in algal blooms is also monitored in the event of a density exceeding acceptable thresholds leads to the closure of the commercial shellfish fishery [4]. The awareness of citizens is also taken into consideration, whose people with asthma or other respiratory problems are recommended to stay away from the beaches during the red tides [131]. In contrast, the treatment of intoxication with brevetoxin is beneficial, it is symptomatic, wheezing usually responds to inhaled bronchodilators. Particle masks can be used to prevent the inhalation of aerosol toxins are favorable. Clinical signs usually disappear within a few days [4].

*U. The AZP:*

The intoxication remains a rare disease, only 5 cases of intoxication have been reported. Because of the similarity with DSP, it is possible that there is a high percentage of under-reporting. On the other hand, no cases of death have been reported to date [67]. In the context of health safety to protect the consumer, a recommended method of analysis for the detection of AZA in aquatic environments has been prescribed mainly by the EU, such as LCMS/MS tandem mass spectrometry liquid chromatography. As for the DSP, there is no specific antidote for IAZA: the treatment is therefore only symptomatic and complementary [42].

## V. CONCLUSION:

In the light of the information gathered in this review of the literature dealing with some toxins synthesized by marine microorganisms, a set of findings were drawn “Table 1”. Over the past three decades, phycotoxin levels have increased dramatically, and they are now omnipresent in all the world’s oceans and seas. Having a detrimental impact on human health through the consumption of seafood and by inhalation, and on fish, birds and marine mammals that are sensitive to these toxins and have, moreover, recorded high rates of morbidity and mortality. All this has raised the alarm. It cannot be denied that this goes directly to human activities that contribute to the creation of conditions conducive to the proliferation of these microalgae. Nevertheless, almost all countries in the world have established regulatory limits of findings for each toxin and monitoring programs for seaweed levels worldwide. It is claimed that in the future there would be more clever approaches.

**TABLE 1: SUMMARY OF INFORMATION ON THE DIFFERENT TYPES OF TOXINS, THEIR ORIGINS, VECTORS, TYPES OF POISONING, SYMPTOMS AND THEIRMODE OF ACTION**

| Toxine | Origin | Vector | Syndrome / intoxication | Symptoms | Mode of action |
|---|---|---|---|---|---|
| Domoic acid | -Diatoms *Pseudonitzschia | Seafood | Amnesic poisoning by seafood | gastrointestinal disorders, nausea, vomiting, abdominal cramps, diarrhea Transient amnesia, dizziness, disorientation, memory loss, coma, death | Kainate glutaminergic receptor agonist |
| Acideokadaïque | -Sponges: *Halichondria spp. , (H. okadaï) -Dinoflagellates: *Dinophysis spp. (D. genus), (D. Fortti) *Prorocentrum spp. ( P. lima) | Seafood | Diarrhetic poisoning by Seafood | Diarrhea, abdominal cramps, nausea, vomiting, dizziness, seizures, hallucinations, short-term memory loss | Serine / threonine inhibitors, protein phosphatase (PP1) and (PP2) |
| Brevétoxines | - Dinoflagellates *Karenia spp., (K. brevis) , (K. mikimotoi), (K.brevisulcata), (K. selliformis ), (K.papilionacea) | Seafood | Neurological poisoning by seafood | Nausea, abdominal cramps, weakness movement difficulties, paralysis, convulsions, coma, death | Unusual opening of voltage-gated sodium channels via orphan S5 receptors |

| | | | | | |
|---|---|---|---|---|---|
| | –Raphidophytes<br>*Chatonella spp. | | | | |
| Saxitoxines | -Dinoflagellate<br>*Alexandrium spp.,<br>*Gymnodinium spp.<br>* Pyrodinium spp.<br>-Cyanobacteria,*Anabaena spp.,,<br>*Aphanizomenon spp.,<br>*Cylindrospermopsis spp.,<br>*Lyngbya spp,.<br>*Planktothrix spp. | Seafood, Fish | Paralyzing seafood poisoning | Tingling / numbness around the lips, neck, face, Tingling with the fingertips, headache, sometimes increased salivation, vomiting, nausea, diarrhea. paraesthesia of the face, lips and tongue, arms and legs, inconsistent speech, dizziness / floating feeling, ataxia, dysphagia, changes in mental state, respiratory failure (paralysis of the diaphragm and muscles of the chest wall), death | Block voltage-gated sodium channels by attaching to site 1 |

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