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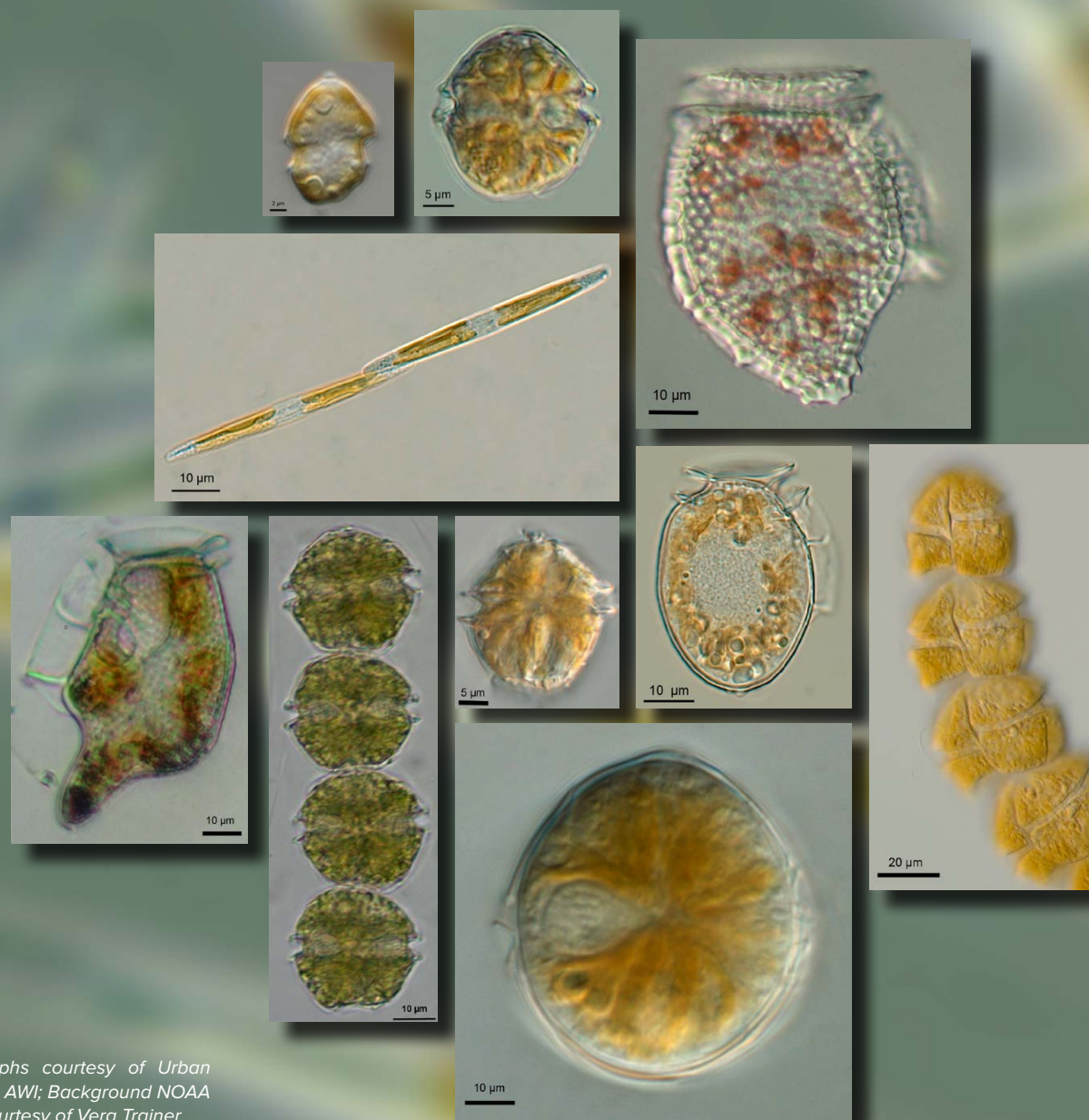
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# Occurrence of MARINE BIOTOXINS AND SHELLFISH POISONING EVENTS and Their Causative Organisms in Argentine Marine Waters

By Bernd Krock, Martha E. Ferrario, Rut Akselman, and Nora G. Montoya



Micrographs courtesy of Urban Tillmann, AWI; Background NOAA photo courtesy of Vera Trainer

**ABSTRACT.** In the Argentine Sea, marine phycotoxins of microalgal origin associated with five shellfish poisoning syndromes have been reported. The most problematic in terms of toxicity and geographic distribution is paralytic shellfish poisoning (PSP), followed by diarrhetic shellfish poisoning (DSP). In contrast, amnesic shellfish poisoning (ASP), spiroimine shellfish poisoning (SSP), and azaspiracid shellfish poisoning (AZP) have not been reported to cause human illness or closures of shellfish harvest sites in Argentina to date but pose a potential risk, as associated toxins and producing organisms are present in Southwest Atlantic waters and were detected at subregulatory levels in mollusks. *Alexandrium catenella* and *Gymnodinium catenatum* have been identified as producers of the PSP toxins C1/2, gonyautoxins (GTX1-4), saxitoxin (STX), and neosaxitoxin (NEO) in the Argentine Sea. Nine potentially toxigenic species of the diatom genus *Pseudo-nitzschia* have been reported for Argentinean coastal waters: *P. australis*, *P. brasiliana*, *P. delicatissima*, *P. fraudulenta*, *P. multiseriata*, *P. pseudodelicatissima*, *P. pungens*, *P. seriata*, and *P. turgidula*, all of which are known to produce the neurotoxin domoic acid that causes ASP. Two genera have been identified as producers of DSP toxins in Argentina: the benthic dinoflagellate *Prorocentrum lima* and several species of the pelagic dinoflagellate genus *Dinophysis*: *D. acuminata*, *D. caudata*, *D. fortii*, *D. norvegica*, and *D. tripos*. The occurrence of these species in Argentine waters is associated with okadaic acid (OA), dinophysistoxin-1 (DTX-1), pectenotoxin-2 (PTX-2), and pectenotoxin-2 seco acid (PTX-2sa). Historically, yessotoxins (YTXs) were also included in DSP syndrome and all three known YTX-producers have been confirmed in Argentinean waters: *Gonyaulax spinifera*, *Lingulodinium polyedra*, and *Protoceratium reticulatum*, but of these only *P. reticulatum* could be associated with YTX production to date. Several species of the family Amphidomataceae, which cause AZP, have been reported for Argentina: *Amphidoma languida*, *Azadinium dexteroporum*, *Az. luciferelloides*, *Az. poporum*, and *Az. spinosum*. In Argentinean coastal waters, out of these species only *Az. poporum* has been identified as toxigenic to date, as it produces azaspiracid-2 (AZA-2) and its phosphorylated form. Currently in Argentina, seafood is monitored for the risk of ASP, AZP, DSP, and PSP.

## INTRODUCTION

Toxic marine microalgae are usually responsible for human shellfish poisoning events. They produce secondary metabolites that may be taken up and concentrated to high levels by filter-feeding mollusks and cause severe illnesses or even death in vertebrates (including humans) after consumption of contaminated shellfish. Interestingly, these marine biotoxins usually trigger no or few adverse effects in primary consumers of toxic microalgae, such as crustaceans and mollusks. The low toxic effect of marine biotoxins on their direct predators seems to argue against the function of marine biotoxins as a defense mechanism against predation. In fact, the ecological function of marine biotoxins is still unknown. We do know that the phycotoxins produced by microalgae are easily accumulated and concentrated by filter-feeding marine

organisms, among which shellfish are the most relevant for humans.

Shellfish poisoning events are categorized according to the symptoms they induce in humans. Although not all types of shellfish poisoning syndromes have been reported to date in Argentine waters, several toxigenic microalgal species and their toxins have been identified in this region during the last four decades. They cause five different shellfish poisoning syndromes:

1. Amnesic shellfish poisoning (ASP; Montoya et al., 2000, 2008; R.M. Negri et al., 2004; Sastre et al., 2007; Cadaillón, 2012; Krock et al., 2015a; Almandoz et al., 2017),
2. Paralytic shellfish poisoning (PSP; Carreto et al., 1981, 1986, 1998, 2007; Esteves et al., 1992; Benavides et al., 1995; Akselman et al., 1998; Gayoso, 2001; Montoya et al., 2006, 2018;

- Santinelli et al., 1994a, 2002; Cadaillón, 2012; Sunesen et al., 2014; Krock et al., 2015a),
3. Spiroimine shellfish poisoning (SSP) (Almandoz et al., 2014; Fabro et al., 2017),
4. Diarrhetic shellfish poisoning (DSP; Gayoso et al., 2002; Sar et al., 2010, 2012; Montoya et al., 2011; Sunesen et al., 2014; Gracia Villalobos et al., 2015; Krock et al., 2015a; Turner and Goya, 2015; Akselman et al., 2015; Fabro et al., 2015, 2016), and
5. Azaspiracid shellfish poisoning (AZP; Turner and Goya, 2015; Tillmann et al., 2016).

This review compiles the recent knowledge on the occurrence of toxigenic microalgae and their phycotoxins in this region.

## PARALYTIC SHELLFISH POISONING (PSP)

PSP toxins are among the most toxic marine biotoxins. In addition to causing muscular paralysis, they have been responsible for hundreds of human fatalities (Hallegraef, 1995). Comprising a group of hydrated purine derivatives, variations consist of hydroxylation at N1, sulphatation at C11, and various substitutions at C13, which can be hydroxylation (decarbonyl toxins), carbamoylation (carbamoyl toxins), *N*-sulfo-carbamoylation (*N*-sulfo-carbamoyl toxins), benzoylation (benzoyl toxins), and all combinations of these substitutions (Figure 1a). Due to two guanidine moieties in the molecule, PSP toxins are charged and thus highly hydrophilic in contrast to most other phycotoxins. The positive charges and the structural configuration of PSP toxins enable them to efficiently bind to and block voltage-dependent ion channels in neuronal cells, which inhibits sodium influx into excited cells and thus inhibits signal relaxation (Hall et al., 1987).

The intraperitoneal toxicity of saxitoxin (the most potent of the PSP toxins) in mice (LD<sub>50</sub>) is 8 µg kg<sup>-1</sup> body weight (Baden et al., 1995). However, toxicity of

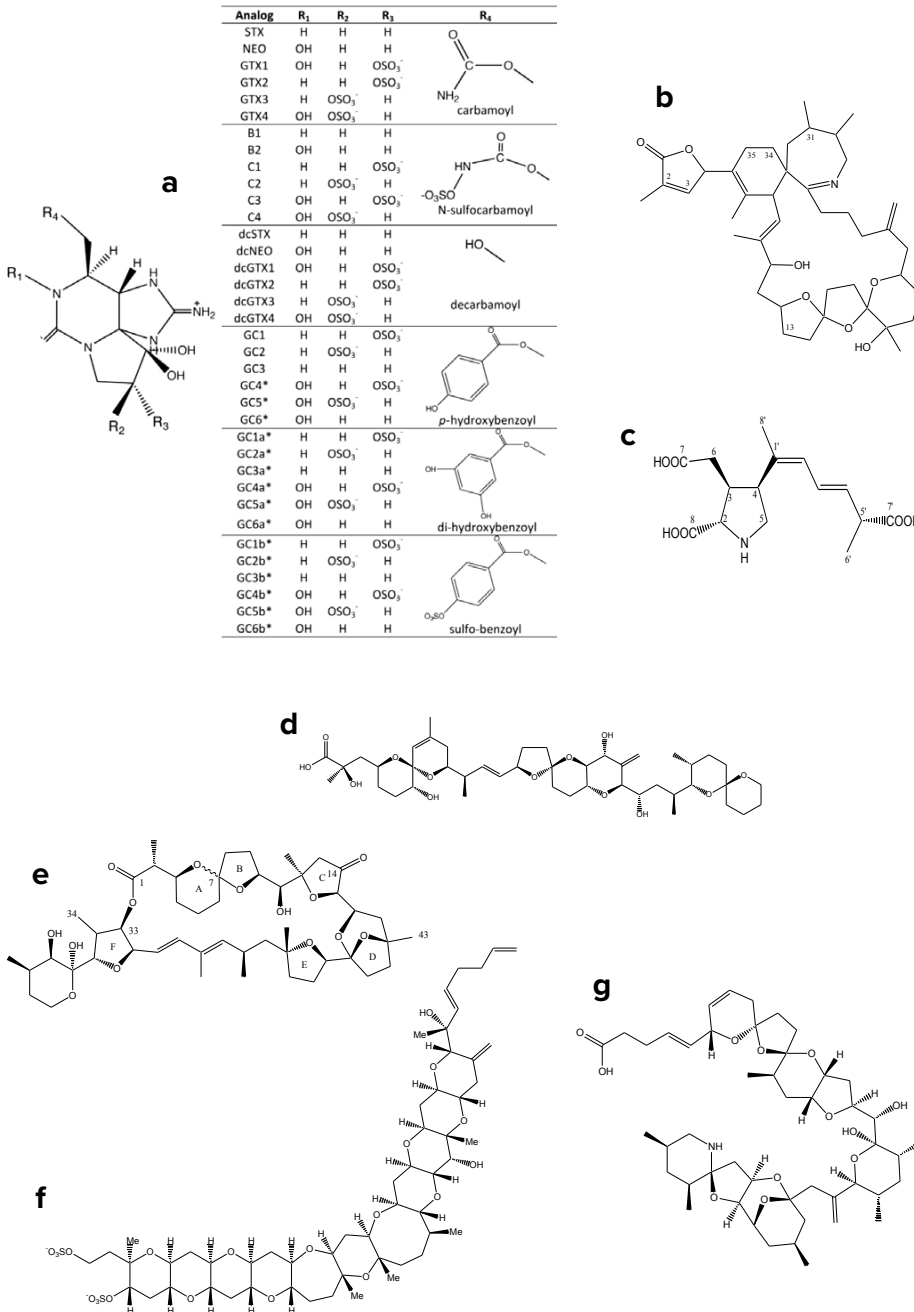
individual variants can differ over more than two orders of magnitude, depending on the net charge of the toxins and their structural configuration. In contrast to many other marine biotoxins, which show a lower oral than intraperitoneal toxicity, both routes of application are efficient for PSP toxins, and thus PSP toxins are considered a high risk for shellfish consumers (Hallegraeff, 1995).

For this reason, monitoring of biotoxins in mollusks is important in the regulation of seafood (Etheridge, 2010).

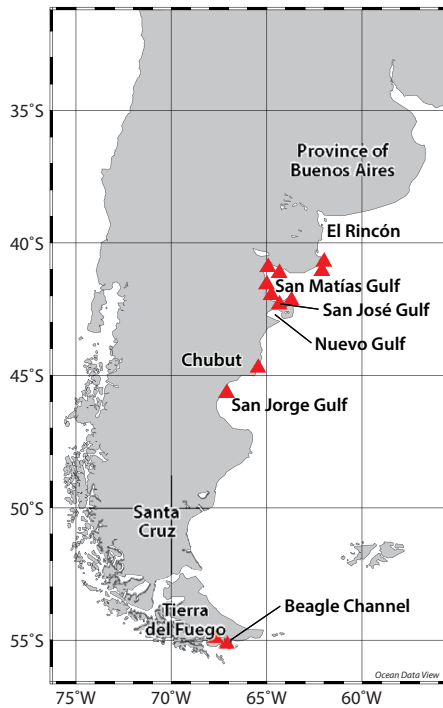
Unpredictable toxic blooms often affect both commercial harvest areas and aquaculture facilities. In addition to seafood regulation and monitoring of shellfish for biotoxins, in many cases phytoplankton monitoring has been established as a preventive measure, as

recommended by the European Union Toxicology Working Group (WG; FAO, 2006). To comply with European regulations and to ensure consumer protection, monitoring of toxic phytoplankton in the water and PSP toxins in shellfish is a statutory requirement for EU member states and for others desiring to export shellfish products to countries within the EU (Anonymous, 2004a).

Sanitary standards for the export of live bivalve mollusks from Argentina are based on Regulation (EC) No. 853/2004 regarding the regulated toxins and their respective legislated limits. The control system and monitoring of toxins in Argentina was initiated in 1980, after lethal poisonings of two fishermen caused by consumption of PSP-contaminated mussels off Valdés Peninsula. The National Service for Health and Agro-Food Quality (SENASA) is responsible for classification and monitoring of shellfish harvest areas and for decisions regarding closures of these areas (Resolution SAGPyA 829/06). SENASA coordinates this work with provincial and regional governments. Each region has a Prevention and Control Plan that includes, in addition to the monitoring of toxic species, the control of toxins in bivalve mollusks. Species of commercial interest in Argentina are common mussels (*Mytilus edulis platensis*), mussels (*Aulacomya ater*), clams (*Ameghinomya antiqua*), geoduck (*Panopea abbreviata*), oysters (*Ostrea puelchana*), scallops (*Aequipecten tehuelchus*, *Zygochlamys patagonica*), razor clams (*Ensis macha*, *Solen tehuelchus*), and gastropods (*Zidona dufresnei*, *Adelomelon beckii*). The local legislation establishes a maximum level of  $<800 \mu\text{g STXeq kg}^{-1}$  per edible part, and this limit is tested weekly in the areas that are classified as extraction and production areas (Figure 2) using the mouse bioassay (MBA; AOAC method 959.08; AOAC, 2005). When PSP exceeds the maximum permitted limit (MPL), the corresponding area is closed for shellfish harvest until shellfish toxicities are assessed as safe again.



**FIGURE 1.** (a) Chemical structures of PSP toxins, (b) 13-desmethyl spirolide C (SPX-1), (c) domoic acid (DA), (d) okadaic acid (OA), (e) pectenotoxin-2 (PTX-2), (f) yessotoxin (YTX), and (g) azaspiracid-1 (AZA-1).



**FIGURE 2.** Map of the study area in Argentina. Red triangles indicate classified shellfish harvesting areas.

Three dinoflagellate genera are known to produce PSP toxins in the marine environment: (1) *Alexandrium*, which has a broad geographical distribution from polar to subtropical waters worldwide (Anderson et al., 2012); (2) *Pyrodinium bahamense*, which is constrained to tropical waters (Harada et al., 1982; Usup and Azanza, 1998); and (3) *Gymnodinium catenatum*, which ranges from tropical to warm-temperate environments (Trainer et al., 2010). There is an early report of a toxic shellfish event in Belgium caused by *Pyrodinium phoneus* (Woloszyńska and Conrad, 1939), which was later inferred to be *Alexandrium ostenfeldii* (Balech, 1995). Among the PSP-producing marine dinoflagellates, *G. catenatum* is distinctive because in addition to the classical PSP toxins it also produces a large variety of benzoyl variants, so-called GC-toxins (A.P. Negri et al., 2007).

*Gymnodinium catenatum*, the first PSP-producing species recorded in Argentina (Balech, 1964), has only been found during the autumn in northern coastal waters off Buenos Aires (Akselman et al., 1998; Montoya et al., 2006; Sunesen

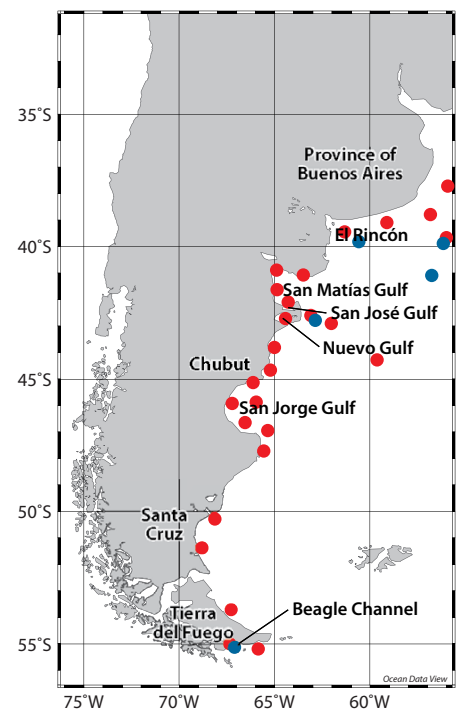
et al., 2014). However, several toxic species of *Alexandrium* have been documented in the Southwest Atlantic for many decades (Balech, 1995; Carreto et al., 1981, 1998; Benavides et al., 1995; Sastre et al., 1997; Santinelli et al., 2002; Akselman et al., 2008).

The dominant PSP-producing species in the Argentine Sea is *Alexandrium catenella*, initially described as *Gonyaulax excavata*, later re-identified as *Alexandrium tamarense*, and very recently recognized as *Alexandrium catenella* following ribosomal phylogenetic studies (John et al., 2014; Prud'homme van Reine, 2017). Blooms of *A. catenella* have been detected frequently since 1980 and were recorded in a latitudinal gradient from the Province of Buenos Aires to the Beagle Channel in almost the entire coastal ecosystem (Figure 3; Carreto et al., 1981; Esteves et al., 1992; Benavides et al., 1995; Akselman, 1996; Carreto et al., 1998; Gayoso and Fulco, 2006; Montoya et al., 2010; Krock et al., 2015a; Fabro et al., 2017; Montoya et al., 2018). Such blooms have been recorded annually through spring and summer seasons from South Patagonia all the way up to Uruguay (Carreto et al., 1998, 2007; Méndez et al., 2001).

Another potentially PSP-producing *Alexandrium* species is *Alexandrium ostenfeldii*, which has been reported to be a PSP producer in some coastal and estuarine regions (Kremp et al., 2014). Though this species was also observed in the Beagle Channel, it was found not to produce PSP there (Almandoz et al., 2014). Very recently, however, *A. ostenfeldii* was associated with PSP toxins detected in San Matías and San Jorge Gulfs and in shelf waters close to Valdés Peninsula (42°–43°S; Fabro et al., 2017). During the same survey, *Alexandrium* aff. *minutum* was detected in shelf waters south of the Province of Buenos Aires and east of Valdés Peninsula (40°–44°S; Fabro et al., 2017). *Pyrodinium bahamense* has not been found to occur in the Argentine Sea.

Several Argentinean PSP events have been documented since 1980 that in

some cases have led to fish, bird, and whale mortalities and even human deaths (Elbusto et al., 1981; Carreto et al., 1981, 1986; Vecchio et al., 1986; Andrinolo et al., 1999; Benavides et al., 1995; Montoya et al., 1996, 1998, 2018; Uhart et al., 2004; Montoya and Carreto, 2007; Wilson et al., 2015). Toxin profiles of several isolates of Argentinean *A. catenella* have been analyzed and found to be mostly dominated by the *N*-sulfocarbamoyl variants C1/C2 and gonyautoxins GTX1/GTX4, GTX2/GTX3; the carbamoyl variants saxitoxin (STX) and neosaxitoxin (NEO) were minor components of these profiles (Carreto et al., 1996, 2001; Montoya et al., 2010; Krock et al., 2015a). Toxin profiles of *A. aff. minutum* to date have not been analyzed. There is one report of toxin profiles in a *G. catenatum* bloom near Mar del Plata (Province of Buenos Aires, 38°S) consisting of 82% decarbamoyl toxins C1/C2 (Montoya et al., 2006). All other detected toxins (GTX2/3, GTX4 and decarbamoyl GTX2/3) were



**FIGURE 3.** Red dots indicate the geographic location of records of the occurrence of paralytic shellfish poisoning (PSP) events and/or potentially PSP-producing species in the Argentine Sea. Blue dots indicate geographic locations of records of the occurrence of *A. ostenfeldii* and SPX.

minor components of the toxin profile, below 10% each. The field samples were also tested for some benzoyl GC toxins (GC1-3) with negative results (Montoya et al., 2006). As GC toxin variability meanwhile has been proven to be much higher than the three tested variants, it cannot entirely be ruled out that *G. catenatum* populations in the Argentine Sea also produce benzoyl GC toxins, as reported for most other parts of the world. But it is noteworthy that eventually in planktonic field populations of the Argentine Sea, PSP profiles other than those of the well-characterized Argentinean *A. catenella* isolates were detected (Montoya et al., 2010; Fabro et al., 2017). This finding indicates that either PSP-producing species other than *A. catenella* are present or that other *A. catenella* strains exhibit different toxin profiles. Certainly, more research is needed to fully assess and understand the presence of PSP-producing species in Argentinean waters.

### SPIROIMINE SHELLFISH POISONING (SSP)

Cyclic imines comprise a large group of toxin classes consisting of spirolides (SPX), gymnodimines (GYM), pinnatoxins, pteriatoxins, prorocontrolides, and spiro-prorocentrimines. Spiroimines, like most lipophilic marine biotoxins, are polyketides; they have a macrocycle as well as a six-membered cycloimine moiety (Cembella and Krock, 2008). GYM are structurally very similar to SPX (Figure 1b), but with an average molecular weight of 500 Da they are approximately 200 Da smaller than SPX. GYM and SPX are thus collectively related to SSP, based on their blocking of muscarinic acetylcholin receptors, which negatively affects neuromuscular, sensory, digestive, and respiratory systems (Gill et al., 2003; Cembella and Krock, 2008; Guéret and Brimble, 2010). Spiroimines are also known as “fast-acting toxins” because of instantaneous reaction in rodents after injection (Wright and Cembella, 1998). Their intraperitoneal toxicity (LD<sub>50</sub>) in

mice was determined as 40 µg kg<sup>-1</sup> body weight, whereas oral toxicity was found to be one and a half orders of magnitude higher (1 mg kg<sup>-1</sup>; Munday et al., 2012).

It is important to note that there is no evidence of harmful effects in humans caused by cyclic imines, as there is for other marine biotoxins, and that the toxic potential of cyclic imines by oral administration is significantly lower than after intraperitoneal administration. The significance of these toxins to food safety is unclear. The report by the European Union Toxicology WG (FAO, 2006) provides evidence that spirolides could be toxic to humans and that further studies are required. Based on the current lack of historical information from regulatory programs regarding human illness and the risk assessment provided by the Expert Consultation, the WG recommends not setting limitations for any of the cyclic imine toxins in the Codex Standard at this time (EFSA, 2010). In Argentina, SPX and GYM are not yet included in the list of regulated toxins.

Benthic or epiphytic members of the dinoflagellate genus *Prorocentrum* produce prorocontrolides and spiro-prorocentrimine (Torigoe et al., 1988; Lu et al., 2001). Pinnatoxins and pteriatoxins initially were found in the bivalve shellfish *Pinna muricata* (Uemura et al., 1995) and *Pteria penguin* (Takada et al., 2001), but it was later proven that both toxin groups were shellfish metabolites of pinnatoxins produced by the dinoflagellate *Vulcanodinium rugosum* (Rhodes et al., 2011). SPX are produced by *Alexandrium ostenfeldii* (Cembella and Krock, 2008), which to date is the only species known to produce this toxin class. *Alexandrium peruvianum*, which has been reported as a spiroimine-producing dinoflagellate (Van Wagoner et al., 2011), is currently assumed to be conspecific with *A. ostenfeldii* (Kremp et al., 2014). To complicate the scenario even more, *A. ostenfeldii* has recently been reported to also be a producer of GYM (Van Wagoner et al., 2011), which until then only had been reported from some species of the genus *Karenia*

(Seki et al., 1995).

In Argentina, information on species producing spiroimine toxins is very scarce. Toxic strains of *A. ostenfeldii* isolated from the Beagle Channel (55°S) were proven to produce 20-methyl spirolide G, 13-desmethyl spirolide C (SPX-1), and two more yet uncharacterized SPX (Almandoz et al., 2014). Nevertheless, SPX-1 has been detected in very low concentrations in shellfish harvested along the entire Argentine coast in all provinces from Buenos Aires (36°S) to Tierra del Fuego (55°S) (Turner and Goya, 2015), suggesting widespread distribution of this dinoflagellate (Figure 3). Recently, *A. ostenfeldii* has been reported in coastal and open shelf waters of the Argentine Sea associated with SPX-1 and 20-Methyl spirolide G (Fabro et al., 2017), interestingly, the same SPX variants produced by the isolates from the Beagle Channel (Almandoz et al., 2014). Even though GYM are widely distributed globally, to date there are no records of GYM in the Southwest Atlantic.

### AMNESIC SHELLFISH POISONING (ASP)

ASP is caused by the rare amino acid domoic acid (DA). DA is structurally similar to glutamic acid (Figure 1c) and thus acts as a glutamic acid agonist that binds to glutamic acid receptors in the brain. This causes neuronal firing due to the inability of glutamate transporters to clear DA from the synaptic cleft, thus prolonging neuronal excitation. Neurotoxicity comprises neurobehavioral effects and loss of short-term memory (Pulido, 2008). The toxicity of DA in mice was assessed as 2.4 mg kg<sup>-1</sup> body weight (LD<sub>50</sub>; Jeffrey et al., 2004). According to EU Regulation 854/2004/EC (Anonymous, 2004b), shellfish production areas are periodically monitored to detect the presence of toxin-producing plankton and the occurrence of their toxins in live bivalve mollusks. Because many regional regulatory agencies have implemented effective seafood monitoring programs for the detection of DA in shellfish and coastal waters, human

ASP events have not been documented since DA was first detected in 2000. The MPL for DA in mollusks has been set at 20 mg kg<sup>-1</sup>. The analysis method used in Argentina, based on high-performance liquid chromatography with UV detection, is performed once per month in classified areas (Figure 2).

Although DA was reported in 1958 (Takemoto and Daigo, 1958) and repeatedly afterward (Maeda et al., 1986; Zaman et al., 1997) as an insecticidal compound produced by the red alga *Chondria armata* in Japan, the first ASP outbreak in humans did not occur until 1987, in Prince Edward Island, Canada (Wright et al., 1989). Very shortly after, the pennate marine diatom *Pseudo-nitzschia multiseriata* was identified as the DA source of the Prince Edward Island ASP incident (Bates et al., 1989). In the following years, several other species of the genus *Pseudo-nitzschia* were reported to be DA producers (Kotaki, 2008).

Despite the relatively recent appearance of ASP, the toxigenic *Pseudo-nitzschia* species and species complexes were known to occur in Argentinean waters as far back to the 1930s. To date, nine potentially toxigenic *Pseudo-nitzschia* species and species complexes have been reported in Argentinean waters. The first species reported was *Pseudo-nitzschia seriata* (a species without accurate determination up to now for the Argentine Sea and initially named *Nitzschia seriata*), in the southern Southwest Atlantic between 56°S and 59°S in 1937 (Hendey, 1937). In succeeding years, the occurrence of *Pseudo-nitzschia seriata* was reported along the entire Argentinean coastline and in shelf waters from the Beagle Channel in Tierra del Fuego to Mar del Plata in the northern Province of Buenos Aires (Frenguelli, 1939; Balech, 1959, 1964, 1971, 1979; Frenguelli and Orlando, 1959; Muller Melchers, 1959; Carreto and Verona, 1974; Verona et al., 1974; Carreto et al., 1981; Almandoz et al., 2008, 2011). Given that the analysis of *P. seriata* in these references was carried out by light microscope and that

the shape of this species is strongly similar to *P. australis*, and its distribution is restricted to the Northern Hemisphere, it is highly probable that these determinations could be wrong.

More recent analyses of *P. seriata* (Almandoz et al., 2008) performed with SEM were not sufficient to discriminate between *P. seriata* and *P. australis*, indicating the need for additional studies with transmission electron microscopy and molecular analysis. The next species to be reported was *Pseudo-nitzschia australis* in the San Matías Gulf (41°S; Frenguelli, 1939), which later turned out also to be present in the entire Argentine Sea (Hasle, 1965; Lange, 1985) as *P. pseudo-seriata* (Ferrario and Galván, 1989; Sastre et al., 1997, 2001; R.M. Negri and Inza, 1998; Sar et al., 1998; Ferrario et al., 1999, 2002, 2017; Montoya et al., 2000; Santinelli et al., 2002; R.M. Negri et al., 2004; Almandoz et al., 2007, 2011, 2017; Cadaillón, 2012; Krock et al., 2015a).

In 1965, *Pseudo-nitzschia multiseriata* (as *Nitzschia pungens* fa. *multiseriata*) and *Pseudo-nitzschia pungens* were simultaneously reported from Puerto Quequén (38°S, Province of Buenos Aires). In contrast to the previous species discussed, *P. multiseriata* seems to be a more temperate species that has only been reported in northern regions, from the Province of Buenos Aires (37°S) to Nuevo Gulf (42°S, Province of Chubut) (Sastre et al., 1997, 2001; Ferrario et al., 1999, 2002; Montoya et al., 2000; Santinelli et al., 2002; Carreto et al., 2004). Distribution along the entire Argentine coast has been reported for *P. pungens* (Balech, 1976; Lange, 1985; R.M. Negri and Inza, 1998; Ferrario et al., 1999, 2002; Gayoso, 2001; Sastre et al., 2001; Sar et al., 2006; Almandoz et al., 2007, 2017; Sunesen et al., 2009; Cadaillón, 2012; Krock et al., 2015a).

There are only two reports of the *Pseudo-nitzschia delicatissima* complex in Argentinean waters, both only in San Matías Gulf (41°S, Province of Río Negro), published in 1974 (Carreto and Verona, 1974; Verona et al., 1974). Eleven years later, *Pseudo-nitzschia fraudulentata* was

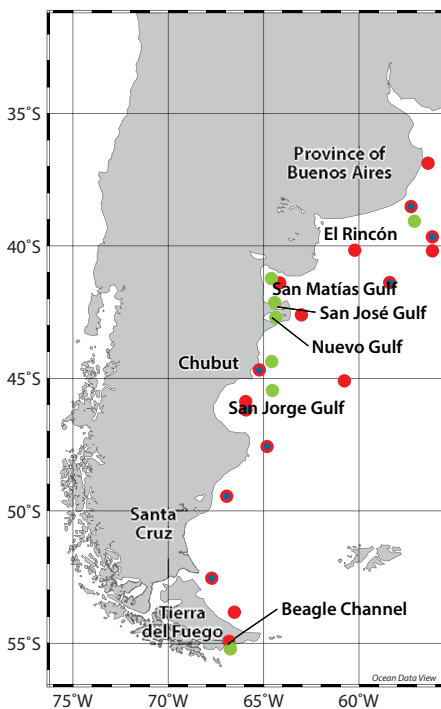
reported (Lange, 1985) and proven to be distributed along the entire Argentinean coastline from 35°S to 54°S (R.M. Negri and Inza, 1998; Ferrario et al., 2002, 2017; Almandoz et al., 2007, 2008, 2011, 2017; Sastre et al., 2007; Cadaillón, 2012).

Detection of the *Pseudo-nitzschia pseudodelicatissima* complex in the Southwest Atlantic dates back to 1998 (R.M. Negri and Inza, 1998); however, for unambiguous species identification of this complex, SEM and in some cases molecular analysis are required, which were not available for most Argentinean reports. Therefore, most records need confirmation. Nonetheless, the reports indicate a distribution along the entire Argentine Sea (Sastre et al., 1997, 2001; Ferrario et al., 1989; Santinelli et al., 2002; Almandoz et al., 2008, 2011 [as *P. calliantha*]; Cadaillón, 2012 [as *P. calliantha*]; Almandoz et al., 2017; Ferrario et al., 2017). *Pseudo-nitzschia turgidula* was also reported in 1998 from the northern Argentine Sea (35°–39°S; R.M. Negri and Inza, 1998), and there are later records from the south (49°–52°S) (Almandoz et al., 2007, 2017). Finally, only one very recent report of *Pseudo-nitzschia brasiliensis* from the northern zone of the Argentine shelf (~39°–40°S) was associated with the presence of low concentrations of DA (Almandoz et al., 2017; Figure 4).

The fact that Argentina has never suffered from human ASP outbreaks is probably due to the extensive expertise in phytoplankton taxonomy and knowledge of the distribution of potentially toxic species in this country. When the DA and *Pseudo-nitzschia* were reported as the cause of the Canadian ASP outbreak in 1987, the presence of *Pseudo-nitzschia* in Argentine waters was already well documented and facilitated the implementation of phytoplankton monitoring and food safety programs. Even though no ASP outbreaks have occurred in Argentina to date, the presence of DA has been confirmed along the entire Argentinean coastline during the last several years, after methods for the specific detection of DA were implemented in the

laboratories related to food regulation. Accordingly, the records of DA detection have a strong bias toward shellfish harvest and production areas, but generally are still scarce.

The first report of DA in Argentina dates to the beginning of this century with the detection of DA in *Pseudo-nitzschia australis* and blue mussels (*Mytilus edulis*) and anchovies (*Engraulis anchoita*) off Mar del Plata (Province of Buenos Aires) (Montoya et al., 2000; R.M. Negri et al., 2004). A second record concerns *Pseudo-nitzschia* detected in the Province of Chubut, specifically Nuevo Gulf (42°S) and Camarones Bay (45°S) (Sastre et al., 2007). The isolation of *P. multiseriis* from coastal waters of the Buenos Aires region confirmed its capacity to produce DA in culture (Montoya et al., 2008). Five years later, DA was reported in phyto- and zooplankton samples of the two North Patagonian gulfs surrounding Valdés Peninsula, San José Gulf and Nuevo Gulf (41°–42°S), indicating for the first time potential vectors of the marine food chain



**FIGURE 4.** Red dots indicate the geographic locations of DSP events and/or potentially toxic *Dinophysis* species; blue dots indicate the occurrence of *P. reticulatum*; green dots indicate where domoic acid (DA) has been reported in the Argentine Sea.

to marine mammals in Argentine waters (Cadaillón, 2012; Willson et al., 2015). During oceanographic expeditions, DA was also detected in phytoplankton further south in the San Jorge Gulf (46°S) and Beagle Channel (55°S) (Krock et al., 2015a) and in San Matías Gulf (41°S) and Nuevo Gulf (42°S) (Almandoz et al., 2017). Very recently, high levels of DA were detected in feces of the Southern Right Whale *Eubalaena australis* (Wilson et al., 2015; D’Agostino, 2017), providing evidence that ASP is a risk not only for humans but also for marine wildlife in Argentina.

### DIARRHETIC SHELLFISH POISONING (DSP)

Historically, when MBA was the only technique available for the detection of marine biotoxins, all lipophilic toxins were regarded as DSP toxins, because they are extracted all together with methanol and, moreover, many of these lipophilic toxins give similar responses in the mouse bioassay. In addition, many of these lipophilic toxins respond to MBA in a similar manner. Traditionally, okadaic acid (OA; Figure 1d), dinophysistoxins (DTXs, which are structural variants of OA), pectenotoxins (PTXs; Figure 1e), and yessotoxins (YTXs; Figure 1f) were regarded as DSP toxins. Recently, however, this classification has been debated. Although they show similar responses in the MBA after intraperitoneal injection, PTXs and YTXs, other than OA and DTXs, do not have diarrhetic effects after oral ingestion (Ogino et al., 1997). In 1980 in Japan, Yasumoto et al. ultimately proved the dinoflagellate *Dinophysis fortii* to be the cause of DSP, but until then the causative compound was still unknown.

OA is a linear polyketide of ca. 800 Da, with several ether rings and a terminal carboxylic acid function (Figure 1d). OA and DTXs have been proven to be specific inhibitors of protein phosphatases 1 and 2a. Symptoms in humans include diarrhetic and tumorigenic effects (Yasumoto and Murata, 1993). LD<sub>50</sub> toxicity of OA in mice was assessed as 204–225 μg kg<sup>-1</sup>

body weight after intraperitoneal injection (Tubaro et al., 2008).

PTXs are structurally related to OA/DTX and feature the same structural elements (Figure 1d,e), but in contrast to OA/DTX, PTXs are lactones and do not have free carboxylic acid groups. However, PTXs are not diarrhetic, despite their structural similarity to OA/DTX, but show cytotoxic and hepatotoxic effects in mammals (Munday, 2008). In general, toxic mechanisms are not well understood, but the LD<sub>50</sub> toxicity (intraperitoneal injection in mice) of the most abundant variant PTX-2 was determined as 219 μg kg<sup>-1</sup> body weight (Munday, 2008).

YTXs are also polyketides, but consist almost completely of condensed ether rings for which they are also called “ladder frame” toxins (Figure 1f). In comparison to OA/DTX and PTXs, they have higher molecular weights (>1,000 Da) and are sulfated compounds. The variability of YTXs is very high with over 90 variants reported (Miles et al., 2005). YTXs share the lack of diarrheticity with PTXs, and their toxic mechanism is not known (Alfonso and Alfonso, 2008). The intraperitoneal toxicity (LD<sub>50</sub>) in mice was determined to be 286 μg kg<sup>-1</sup> body weight, whereas its oral toxicity was found to be more than two orders of magnitude higher (54 mg kg<sup>-1</sup>; Alfonso and Alfonso, 2008).

DSP syndrome is a frequent concern of small-scale shellfish fisheries in Argentina, because it can cause prolonged closure of mussel harvest areas (Turner and Goya, 2015). Monitoring for lipophilic toxins is currently conducted in the country following the EU Harmonised Standard Operating Procedure for detection of lipophilic toxins by the MBA (EURLMB, 2013). Positive MBA results bring closure of harvesting areas, and bans on selling of shellfish from affected areas. Currently, only MBA is used in Argentina for routine monitoring of lipophilic toxins, and very few data are available regarding the identity of the lipophilic toxins responsible for toxicity. Only a few analogues of



each group are legislated, and their quantity has to be referred to the predominant compound of each group, called the reference compound. For OA, the DTX and PTX MPL is 160 µg of OA eq kg<sup>-1</sup>, and for YTX it is 3.75 mg YTX eq kg<sup>-1</sup>.

Originally, OA was isolated from the marine sponge *Halichondria okadai* (Tachibana et al., 1981) after which the compound was named, but shortly thereafter, OA and DTX-1 were reported from the benthic marine dinoflagellate *Prorocentrum lima* (Murakami et al., 1982). PTX was isolated from the scallop *Patinopecten yessoensis* (Yasumoto et al., 1985) and YTX from the same species (Murata et al., 1987). PTX were reported to be produced by *Dinophysis* (Yasumoto et al., 1988), whereas *Protoceratium reticulatum* was identified as a producer of YTX (Satake et al., 1997). In addition, *Lingulodinium polyedra* (Draisci et al., 1999) and *Gonyaulax spinifera* (Rhodes et al., 2006) were later found to be YTX sources.

In Argentina, among the microalgae found to produce OA/DTX and PTX, six species are associated with these toxins, five of which belong to the genus *Dinophysis* (Hoppenrath, 2017; Zingone and Larsen, 2017). *Dinophysis acuminata*, *D. caudata*, and *D. tripos* were cited for the first time by Balech (1988, and references herein), *D. fortii* by Gil et al. (1989), *D. norvegica* by Fabro et al. (2016), and *Prorocentrum lima* by Santinelli et al. (1995). *Phalacroma rotundatum* (as *Dinophysis rotundata*) is quite frequent in this region (Balech, 1988), and while it may contain DSP toxins, it is suspected to be not a *de novo* toxin producer (González-Gil et al., 2011; Figure 4).

Whereas the occurrence of *D. norvegica* seems to be constrained to southern Argentine waters (>52°S; Fabro et al., 2016), consistent with its description as a boreal species, *D. acuminata* and *D. tripos* have been found in the entire Argentine Sea (Balech, 1988). *D. acuminata* has been recorded in plankton samples from the Patagonian coasts and North Patagonian gulfs (Gil et al., 1989; Sastre et al., 1990;

Santinelli et al., 1994b, 2002; Santinelli, 2008; Gracia Villalobos et al., 2015), from the San Jorge Gulf (Akselman, 1996), and from middle shelf waters along the Argentine Sea (Fabro et al., 2015), as well as in stomach contents of the commercially exploited scallop *Zygochlamys patagonica* (Schejter et al., 2002), while *D. tripos* was recorded from middle shelf waters (Fabro et al., 2015) and the North Patagonian gulfs (Gracia Villalobos et al., 2015). *D. caudata* is considered a warm water species, but seems to be tolerant in this region (Balech, 1988), having been recorded in San Jorge Gulf in winter (Akselman, 1996). *D. fortii*, first found north of 39°S beyond the shelf margin within waters of the Brazil Current (Balech, 1988), was later recorded in San José Gulf (Gil et al., 1989). *Prorocentrum lima* was recorded in water samples from the North Patagonian San José Gulf and Nuevo Gulf (Gayoso et al., 2002) and from the Beagle Channel in Tierra del Fuego in 2013 (*pers. comms.* from Hugo Benavides, Instituto Nacional de Desarrollo Pesquero, October 20, 2017, and Marcelo Hernando, Comisión Nacional de Energía Atómica, October 26, 2017); it has also been identified as an epiphyte on seaweeds (Gayoso et al., 2002), including the brown alga *Dictyota dichotoma* in San Matías Gulf (Gauna, 2010).

Generally, records of the occurrence of DSP toxins in Argentine waters in the scientific literature are scarce. The first DSP outbreak in Argentina occurred in March 1999, caused by mussels harvested in San José Gulf and Nuevo Gulf (Figure 4). This DSP event was caused by O-acyl esters of DTX-1 (summarized as DTX-3) that were detected in the contaminated mussels (Gayoso et al., 2002). DTX-3 has never been observed in dinoflagellates but is known to form from OA/DTX-1/2 through bivalve metabolic activity (Yasumoto et al., 1985; Quilliam et al., 1996). Despite the recurrent presence of *Dinophysis* in the area, this DSP event was associated with *Prorocentrum lima* (Gayoso et al., 2002).

The first record of an outbreak of

DSP associated with the presence of *Dinophysis* species (*D. acuminata* and *D. caudata*) occurred in 2010 in the Northern Province of Buenos Aires (36°–37°S), expressed in cases of human illness after shellfish consumption (Sar et al., 2010). Samples of the wild clams *Mesodesma mactroides* and *Donax hanleyanus* were contaminated with complex DSP toxin profiles composed of OA, DTX-1, Acyl-OA, and Acyl-DTX-1 (Sar et al., 2012), whereas OA, DTX-1 and PTX2 were detected in plankton samples during this event (Montoya et al., 2011). A comprehensive survey of bivalves undertaken by the Argentine public health program revealed the occurrence of several DSP toxins not only in the Province of Buenos Aires but also in the North Patagonian gulfs, San Jorge Gulf, and Beagle Channel (Figure 4). Detected DSP toxins included OA, DTX-1, DTX-2, PTX-2, and YTX (Turner and Goya, 2015). In more recent reports, PTX-2 was found in the entire Argentine Sea, associated with several *Dinophysis* species (Gracia Villalobos et al., 2015; Krock et al., 2015a; Fabro et al., 2016), and PTX-2 seco acid (PTX-2sa) was associated with *D. tripos* in the northern area (37°–43°S; Fabro et al., 2015).

All three known YTX producers (*Lingulodinium polyedra*, *Gonyaulax spinifera*, and *Protoceratium reticulatum*) have been reported in Argentine waters (Balech, 1988). While *L. polyedra* is rare and has been observed in warm waters influenced by the Brazilian Current, motile stages of *G. spinifera* and *P. reticulatum* are widely distributed, with their cysts found in surface sediments of coastal and mid shelf areas (Akselman, 1996; Akselman et al., 2015; Krock et al., 2015a). However, there were no records of YTX from the Argentine Sea until very recently when YTX was detected in scallops from the Provinces of Buenos Aires (39°S) and Santa Cruz (46°S) (Turner and Goya, 2015) and in plankton from San Jorge Gulf (Akselman et al., 2015; Krock et al., 2015a). In addition, Akselman et al. (2015) describe the YTX

profiles of two *P. reticulatum* isolates from the San Jorge Gulf, consisting of >95% YTX and some variants in minor quantities. Comparison of species abundances and YTX levels in planktonic samples suggests that *G. spinifera* did not contribute to YTX levels found in the San Jorge Gulf (Akselman et al., 2015).

## AZASPIRACID SHELLFISH POISONING (AZP)

AZP is the most recently described shellfish poisoning syndrome. Like many dinoflagellate toxins, azaspiracids (AZAs) are large polyethers in the mass range of approximately 700 Da to 900 Da. AZA structure is characterized by a long carbon chain with several rings generated by the formation of ether rings, an amino function in the terminal ring, and a carboxylic acid at the other side of the molecule (Figure 1g). To date, more than 50 AZA variants have been reported. This high diversity is partly due to biosynthetic variation in dinoflagellate biosynthesis and also to metabolic activity of accumulating bivalves (Hess et al., 2014). Studies reveal several cytotoxic effects of

AZA, such as on arrangement of F-actin, on cytoskeleton, and on increase of cytosolic calcium levels in lymphocytes. But the mechanisms responsible for diarrheagenic and tumorigenic effects in vertebrates are not yet well understood (Twiner et al., 2014). The LD<sub>50</sub> toxicity of AZA-1 in mice after intraperitoneal injection was determined as 0.2 µg kg<sup>-1</sup> body weight (Twiner et al., 2014).

The first documented AZP event occurred in The Netherlands in 1995, when eight people became ill after the consumption of Irish mussels (McMahon and Silke, 1996). In the following years, AZA-1 was identified as the causative compound (Satake et al., 1998), and more AZA variants were subsequently detected in shellfish (Ofuji et al., 1999; James et al., 2003). Because AZAs belong to the group of large polyketides, they were suspected to be of phytoplanktonic origin. However, the producing organisms remained unknown until a small marine dinoflagellate of the newly identified genus *Azadinium* was proven to be capable of the *de novo* synthesis of AZA (Krock et al., 2009; Tillmann et al., 2009).

To date, four species of the family Amphidomataceae are known to produce AZA: *Azadinium spinosum* (Krock et al., 2009), *Azadinium poporum* (Krock et al., 2012, 2015b), *Amphidoma languida* (Krock et al., 2012), and *Azadinium dexteroporum* (Percopo et al., 2013; Rossi et al., 2017). Huge blooms of *Azadinium* cf. *spinosum* were reported in Argentinean shelf margin and mid-shelf waters (38°30'–41°S) in 1990 and 1991 (Akselman and Negri, 2012), and again in 1998 (Akselman et al., 2014), before the genus *Azadinium* was described, and AZP was unknown. After a more thorough study of archived material of the 1991 bloom, it became obvious that the blooming organism in fact was a new species, *Azadinium luciferelloides*. It was assumed that the other 1990s blooms were also dominated by this species (Tillmann and Akselman, 2016). In addition to *Az. luciferelloides*, several species of amphidomataceans co-occurred in the 1991

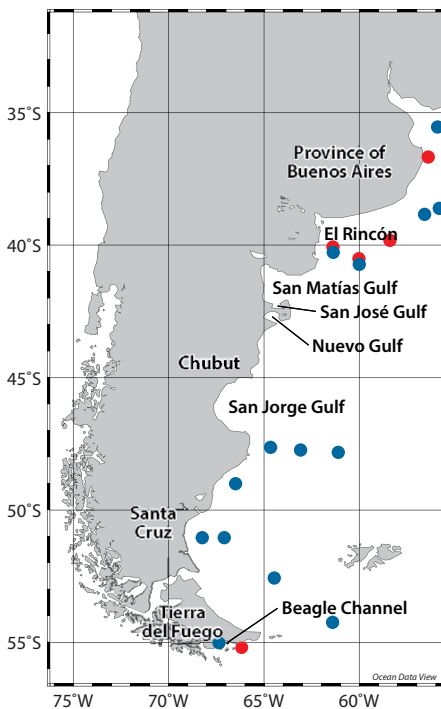
bloom, including the toxigenic *Az. spinosum*, *Az. dexteroporum*, and *Am. languida* (Tillmann and Akselman, 2016).

To date, nothing is known about the toxicity of *Az. luciferelloides*, nor is anything known about the possible production of toxins by the other species identified in the same water mass. Cultures are needed to evaluate their AZA production potential because it is known that toxin production can be variable among strains of a single species (e.g., Gu et al., 2013). Traces of AZA-2 were detected in yellow clams (*Mesodesma mactroides*) and mussels (*Brachidontes rodriguezii*) from the Northern Province of Buenos Aires (37°S) in 2008 (Turner and Goya, 2015). This is consistent with the occurrence of AZA-2 producing *Azadinium poporum*, which was isolated from resting stages (dinocysts) from El Rincón area (40°S). Interestingly, in addition to AZA-2, these isolates also produce a phosphorylated form of AZA-2—the first report of a phosphorylated marine biotoxin (Tillmann et al., 2016).

Several species of amphidomataceans were identified in plankton samples collected across a geographic range from the San Jorge Gulf to Tierra del Fuego in autumn 2004 and spring 2005 (author Akselman, unpublished), along with a dinoflagellate whose morphology is similar to *Azadinium* in the Beagle Channel (Ferrario et al., 2017), records that are complemented by the detection of AZA-2 in plankton samples from the eastern mouth of Beagle Channel (author Krock, unpublished; Figure 5). The very recent discovery of toxic *Azadinium* and the recorded diversity of Amphidomataceae in Argentina, which include toxigenic and non-toxigenic species, poses a potential health risk; thus, more knowledge about their geographic distribution and their production of AZA is needed.

## CONCLUSION

In comparison to its neighbor Chile, Argentina has not been affected as heavily by harmful algal blooms (HABs). This is partly due to the fact the Argentinean



**FIGURE 5.** Red dots indicate the occurrence of azaspiracids (AZA) and blue dots of *Azadinium* in the Argentine Sea.

shellfish production is far less but also subject to different hydrodynamic conditions, which in the Southwest Atlantic generally are less favorable for mass proliferation of HAB species. To date, human poisonings only have been reported for PSP and DSP, the former being the most notorious, for both its high toxicity and the ubiquitous distribution of species that produce it in the Southwest Atlantic. It is noteworthy that the highest global toxicity value (up to 127,000 µg STX eq. 100 g<sup>-1</sup> in mussel) was recorded in Beagle Channel (Ushuaia) during an intense bloom of *A. catenella* (Benavides et al., 1995). The other three syndromes (ASP, AZP, and SSP) have not yet led to human poisonings, but the presence of the causative species and their associated toxins pose a potential risk for these syndromes. To assess the HAB risk to living marine resources under a warming climate, more research is needed to better understand the conditions that favor proliferation of HAB species as well as locally occurring toxin profiles and their specific toxicities. ☒

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