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To cite this version:

Mireille Chinain, Clémence M Gatti, Hélène Martin-Yken, Mélanie Roué, H Taiana Darius. Ciguatera poisoning: an increasing burden for Pacific islands communities in light of climate change?. Pr Luis Botana. Climate Change and marine and freshwater toxins, 2nd edition, inPress. hal-02945267

HAL Id: hal-02945267
https://hal.inrae.fr/hal-02945267
Submitted on 22 Sep 2020

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1 Introduction

Harmful algal blooms (HABs) are natural phenomena that have apparently expanded worldwide in recent decades (Van Dolah, 2000; GEOHAB, 2001; Hallegraeff, 2010). They can cause damage to the environment, alter marine food webs and threaten seafood safety and human health (Erdner et al., 2008; Berdalet et al., 2016; Sanseverino et al., 2016), thus causing significant socioeconomic problems most notably among world populations that rely heavily on marine resources for their subsistence (Bell et al., 2009). It is suggested that this observed HAB increase is linked to both anthropogenic influences on the biosphere and naturally occurring environmental changes such as climate change (Hallegraeff, 1993, and references therein; Anderson et al., 2008; Gobler et al., 2017), and that current projections of water temperature warming will eventually result in even greater problems due to HABs in the future (Marques et al., 2010, and references therein).

Among the many algal toxins that can find their way through marine food webs to human consumers where they cause various poisoning illnesses, are ciguatoxins (CTXs), potent neurotoxins produced by dinoflagellates in the genera *Gambierdiscus* and *Fukuyoa*. Ciguatoxins are responsible for Ciguatera Poisoning (CP), a disease resulting from the consumption of poisonous coral-reef finfish and marine invertebrates (Anderson and Lobel, 1987; Lehane and Lewis, 2000; Darius et al., 2018b). With an estimated occurrence of 10,000 to 50,000 cases per year (Friedman et al., 2008), CP is regarded as the most prevalent non-infectious seafood-borne disease worldwide. This poisonous syndrome is particularly well known to communities of the Pacific Island Countries and Territories (PICTs) where the highest incidence rates (IRs) in the world are consistently reported since the 1970s (Bagnis et al., 1985; Chateau-Degat et al., 2007a; Friedman et al., 2008; Rongo and van Woesik, 2011; Skinner et al., 2011; Chinain et al., 2019). This has prompted extensive studies in various Pacific ciguatera hotspots to assess the genetic diversity and distribution of the causative algal organisms (Chinain et al., 1997; Rhodes et al., 2010; Murray et al., 2014; Xu et al., 2014; Rhodes et al., 2017b; Smith et al., 2017; Darius et al., 2018b; Larsson et al., 2018; Rhodes et al., 2020), the marine species at risk (Halstead, 1978; Kodama and Hokama, 1989; Legrand and Bagnis, 1991; Rongo and van Woesik, 2011; Laurent et al., 2012; Mak et al., 2013; Darius et al., 2018a; Darius et al., 2018b), the suite of toxins involved (Yasumoto et al., 1987; Murata et al., 1990; Holmes and Lewis, 1994; Yasumoto et al., 2000; Satake, 2006; Chinain et al., 2010a; Rhodes et al., 2014; Munday et al., 2017; Larsson et al., 2018; Longo et al., 2019), the socioeconomic impacts on local communities' well-being (Lewis, 1983; Lewis, 1992; Lewis and Ruff, 1993; Rongo and van Woesik, 2012; Morin et al., 2016; Friedman et al., 2017), etc. But, despite significant advances in the understanding of this complex eco-toxicological phenomenon, CP outbreaks are still difficult to predict and the prevalence of this disease dangerously high in PICTs.

The present paper will deal with several ciguatera-related issues specific to PICTs and neighboring countries in the Oceania region. A first section describes the genetic heterogeneity and chemodiversity of *Gambierdiscus* and *Fukuyoa* species occurring in thearea and how climate change is likely to influence CP risk locally as illustrated by the recent expansion of ciguatera to previously unaffected areas. A second section presents the epidemiology of CP in the region and the survey networks currently in place which have allowed identification of novel vectors of ciguatera among marine invertebrates highly prized by local populations. A further section deals with ciguatera perception among Pacific islands communities and the various adaptive strategies and traditional practices developed to cope with this poisoning risk. The fourth and last section addresses the issue of the implementation of monitoring capabilities and risk management programs in PICTs, by highlighting the potential interest and applicability of several monitoring and detection tools particularly well adapted to the context of Pacific islands, and the importance of outreach and communication strategies to modify high risk-taking behaviors among local communities. A concluding section outlines some of the issues that remain to be addressed for increased food safety among the island communities of the Pacific region.

2 Ciguatera poisoning in the context of climate change

2.1 The Oceania region, a "biodiversity hotspot" for *Gambierdiscus* species

2.1.1 Geographical distribution of *Gambierdiscus/Fukuyoa* species in the Oceania region

Among the major locales presently regarded as CP-endemic areas, the Oceania region is likely the area where the diversity and geographic distribution of *Gambierdiscus* and *Fukuyoa* species are best documented. Today, this region continues to be the site of extensive sampling efforts. As a result, five of the eight newly described *Gambierdiscus* species since 2016 originated from various South Pacific locales, *i.e.*, *G. cheloniae* (Smith et al., 2016), *G. honu* (Rhodes et al., 2017a), *G. lapillus* (Kretzschmar et al., 2017), *G. lewisii* and *G. holmesii* (Kretzschmar et al., 2019a), and it is highly likely that additional species will be characterized in the near future, as the genus *Gambierdiscus* is also comprised of four unidentified clades that are genetically distinct and may constitute new undescribed species (Litaker et al., 2009; Nishimura et al., 2013; Xu et al., 2014; Dai et al., 2017). Currently 15 *Gambierdiscus/Fukuyoa* spp. out of the 21 published species are known in the South Pacific, the six species not yet reported in this region being *G. carolinianus*, *G. excentricus*, *G. jejuensis*, *G. silvae*, *F. rutzleri* and *F. yasumotoi*. Table 1 and Figure 1 provide an updated summary of the current distribution of *Gambierdiscus* and *Fukuyoa* species in the Pacific region.

Tab. 1

Fig. 1

From Figure 1, it is clear that several island groups in the Pacific such as Hawaii, French Polynesia, the Cook Islands, the Kingdom of Tonga, the Republic of Kiribati and the Kermadec Islands could represent "biodiversity hotspots" of *Gambierdiscus* with the report of at least five distinct species in each of these island groups (Tab. 1 and references therein): of note, up to six *Gambierdiscus* species were found to co-exist within a single sampling location of Rikitea Bay on Mangareva Island, a long-standing ciguatera hotspot in the Gambier archipelago (French Polynesia) (Chinain et al., 2016). Similarly, eight species are currently known in Australia from tropical Queensland to the more temperate waters of New South Wales.

This increase in species number has raised concerns about the future trends of ciguatera in this CP-prone region, as it is believed that the global distribution of CP will dramatically increase in the coming years in the context of climate change and global warming (Hales et al., 1999; Villareal et al., 2007; Llewellyn, 2010). Indeed, average annual increases in sea water temperatures have been reported for both south-eastern Australia and for New Zealand's coastal waters (New South Wales Government; Ministry for the Environment (Manatū Mō Te Taiao), 2016), consistent with occurrence reports of both *Fukuyoa* and *Gambierdiscus* in the sub-tropical northern region of New Zealand and Kermadec Islands (Rhodes et al., 2017b; Rhodes et al., 2017c; Rhodes and Smith, 2018; Rhodes et al., 2020), and in the more temperate waters of New South Wales, Australia (Kohli et al., 2014; Larsson et al., 2018; Larsson et al., 2019). It has been suggested that blooms of *G. carpenteri* populations stretching as far as 37°S, south of Sidney (New South Wales) may be explained by currents bringing cells from tropical Queensland to the warming New South Wales waters (Kohli et al., 2013; Kohli et al., 2014). It should be noted that recent observations indicate that *Gambierdiscus* and/or *Fukuyoa* spp. are also presently established in other temperate-like areas globally, including Korea (Jeong et al., 2012; Jang et al., 2018), Japan (Nishimura et al., 2016), the northern Gulf of Mexico (Tester et al., 2013), and the Mediterranean Sea (Aligizaki and Nikolaidis, 2008; Tudó et al., 2018). In particular, *G. australes* is among the few species that appear to have the widest latitudinal ranges from 40.00°N to 35.25°S (Tester et al., 2020). But whether this current expansion of the geographic range of *Gambierdiscus*/*Fukuyoa* spp. in South Pacific areas may lead to increasing risk of CP outbreaks locally is still a matter of current debate: *e.g.,* there is no concurrent report of human health impacts in northern New-Zealand, yet (Rhodes et al., 2020), while in New South Wales, there has been an apparent increase in CP from both imported fish and Spanish mackerel (*Scomberomorus commerson*) caught in the region's coastal waters (Farrell et al., 2017; Seger et al., 2019).

2.1.2 Chemodiversity in *Gambierdiscus/Fukuyoa* species from the Oceania region

Gaining detailed insights into the suite of toxins produced by *Gambierdiscus*/*Fukuyoa* spp. is critical to better ascertain the real threat high abundance of populations of these organisms poses to human health. Not all *Gambierdiscus*/*Fukuyoa* species produce CTXs and maitotoxins (MTXs), the main cyclic polyether compounds regarded as the causative agents of CP. It is believed that the production of CTXs is limited to certain genetic species/strains of *Gambierdiscus*/*Fukuyoa* (Chinain et al., 2020, for review and references therein). To date, Pacific-CTXs (P-CTXs) congeners have been formally detected, through isolation and/or liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) analyses, in only two of the 15 *Gambierdiscus* species reported in the Pacific Ocean (Fig. 1), *i.e.*, in *G. polynesiensis* strains from French Polynesia, the Cook Islands and the Kermadec Islands (Chinain et al., 2010a; Rhodes et al., 2014; Roué et al., 2016; Smith et al., 2016; Munday et al., 2017; Murray et al., 2018; Roué et al., 2018c; Sibat et al., 2018; Longo et al., 2019; Rhodes et al., 2020), and in *G. toxicus* strains from French Polynesia (Murata et al., 1990; Satake et al., 1993b; Yasumoto et al., 2000; Yogi et al., 2011) (Tab. 2). However, all strain identifications made before the introduction of molecular analyses in 1999 (Chinain et al., 1999a) should probably be reassessed, particularly concerning the CTX-producing *G. toxicus* from French Polynesia which is most likely a *G. polynesiensis* strain (Soliño and Costa, 2018). For now, none of the P-CTXs searched for by LC-MS/MS (*i.e.*, P-CTX3B, P-CTX3C, P-CTX4A and P-CTX4B) were detected in strains of *G. australes*, *G. carpenteri*, *G. cheloniae*, *G. holmesii*, *G. honu*, *G. lapillus*, *G. lewisii* and *G. pacificus* from Australia, the Cook Islands, French Polynesia, the Kermadec Islands and the Kingdom of Tonga (Rhodes et al., 2014; Kohli et al., 2015; Smith et al., 2016; Kretzschmar et al., 2017; Munday et al., 2017; Rhodes et al., 2017a; Rhodes et al., 2017b; Rhodes et al., 2017c; Larsson et al., 2018; Murray et al., 2018; Rhodes and Smith, 2018; Kretzschmar et al., 2019a; Rhodes et al., 2020), nor in strains of *F. paulensis* from Australia and New-Zealand (Munday et al., 2017; Rhodes and Smith, 2018; Larsson et al., 2019; Rhodes et al., 2020). Moreover, to the best of our knowledge, Pacific strains of *G. balechii*, *G. belizeanus*, *G. caribaeus*, and *Gambierdiscus* sp. type 4 and 5 have not been analyzed for the presence of P-CTXs, yet, using LC-MS/MS. However, using the mouse bioassay (MBA), radioactive receptor binding assay (rRBA), or neuroblastoma cell-based assay (CBA-N2a), CTX-like activities have been evidenced in almost all Pacific species of *Gambierdiscus*, but at ranges well below those reported for *G. polynesiensis* strains (Chinain et al., 2020, for review and references therein).

Tab. 2

Gambierdiscus is also known to produce several other cyclic polyether compounds, which were characterized from Pacific strains for the majority of them. MTX1, for instance, was first isolated from a French Polynesian strain identified as *G. toxicus* (potential misidentification) (Murata et al., 1993), and further detected in numerous *G. australes* strains from the Cook Islands and the Kermadec Islands by means of LC-MS/MS (Rhodes et al., 2014; Kohli et al., 2015; Smith et al., 2016; Munday et al., 2017; Rhodes et al., 2017b;

Rhodes et al., 2017c; Murray et al., 2018; Rhodes and Smith, 2018; Rhodes et al., 2020). The putative MTX2, whose structure has not yet been elucidated, was reportedly found in cultures of *G. toxicus*, *G. caribaeus* and *G. pacificus* from Australia, Hawaii and French Polynesia (Holmes et al., 1990; Holmes and Lewis, 1994; Pisapia et al., 2017b). Of note, a third MTX analogue, named MTX4, has been recently described in *G. excentricus* strains from the Atlantic Ocean (Pisapia et al., 2017b), and efforts to document its production in Pacific strains as well are currently underway. Gambieric acids (GA)-A, -B, -C and -D, gambierol and gambieroxide were isolated from French Polynesian strains also identified as *G. toxicus* (potential misidentifications) (Nagai et al., 1992; Satake et al., 1993a; Watanabe et al., 2013). Interestingly, gambierone, which was originally characterized from a Caribbean *G. belizeanus* strain (Rodríguez et al., 2015), was recently detected in several *G. polynesiensis* strains from French Polynesia using LC-MS/MS (Longo et al., 2019). Finally, the presence of 44-methylgambierone, formerly known as putative MTX3 (Holmes and Lewis, 1994), and whose structure has been fully characterized only recently (Boente-Juncal et al., 2019; Murray et al., 2019), has been demonstrated in almost all *Gambierdiscus* strains/species analyzed from Australia, the Cook Islands, French Polynesia, Hawaii, the Kermadec Islands, and the Kingdom of Tonga, *i.e.*, *G. australes*, *G. caribaeus, G. carpenteri*, *G. cheloniae*, *G. holmesii*, *G. honu*, *G. lapillus*, *G. lewisii*, *G. pacificus*, *G. polynesiensis* and *G. toxicus* (Rhodes et al., 2014; Kohli et al., 2015; Smith et al., 2016; Kretzschmar et al., 2017; Munday et al., 2017; Pisapia et al., 2017b; Rhodes et al., 2017a; Rhodes et al., 2017b; Rhodes et al., 2017c; Larsson et al., 2018; Murray et al., 2018; Rhodes and Smith, 2018; Roué et al., 2018c; Kretzschmar et al., 2019a; Longo et al., 2019; Rhodes et al., 2020), as well as in strains of *F. paulensis* from Australia and New-Zealand (Munday et al., 2017; Rhodes and Smith, 2018; Larsson et al., 2019; Rhodes et al., 2020), thus confirming the ubiquitous character of this compound. Only few temperate clones of *G. carpenteri* from Australia have been found free of 44-methylgambierone (Kohli et al., 2014; Larsson et al., 2018; Murray et al., 2018), while data are not yet available for Pacific strains of *G. balechii*, *G. belizeanus*, and *Gambierdiscus* sp. type 4 and 5.

While CTXs and, to a lesser extent, MTXs are believed to play a prominent role in CP outbreaks, it is not fully understood whether the other metabolites produced by *Gambierdiscus* and *Fukuyoa* spp. could also contribute to the clinical features of ciguatera, but most of them are considered as compounds of interest for their bioactivity and/or potential therapeutic applications (Rubiolo et al., 2015; Boente-Juncal et al., 2019). For instance, GA-A and gambierol are known to act as functional antagonists of the same binding site than CTXs on voltage-gate sodium channels (VGSCs), while gambierone has been shown to cause VGSCs activation in a similar pattern as CTXs, although with much less potency. In addition, both gambierone and 44-methylgambierone are able to induce a small rise in the cytosolic calcium concentration in human cortical neurons as CTXs (Chinain et al., 2020, for review and references therein).

2.2 Ciguatera poisoning occurrences in the context of climate change

2.2.1 Influence of environmental factors

It is well known that reports of CP events/outbreaks are significantly underestimated because of failure to recognize its symptoms (Friedman et al., 2017), limited collection of epidemiological data on a global level (Goater et al., 2011), and even a generalized reticence to report ciguatera in endemic regions (*e.g.*, within island communities) since many patients tend to rely on traditional medicine for treatment (Bourdy et al., 1992; Kumar-Roiné et al., 2011). Moreover, the lack of standardization in data collection methodologies and timelines makes it difficult to compare incidence data across regions. Thereby, it is difficult to conclude whether there has been a global increase in CP incidents frequency over the past decades, and even more difficult to link such observations to climate change impacts.

Many laboratory studies have investigated *Gambierdiscus/Fukuyoa* spp. growth responses and toxin production under varying environmental factors (Parsons et al., 2012; Chinain et al., 2020, for reviews and references therein). Temperature and pH are some of the environmental drivers most representative of climate change, *e.g.*, global ocean warming and acidification (Orr et al., 2005; Intergovernmental Panel on Climate Change (IPCC), 2007; Meehl et al., 2007; Brown et al., 2015; Nurse and Charlery, 2016). The effects of temperature changes are, by far, the best documented in the literature. However, it should be mentioned that many of the previous studies were conducted at a time when *Gambierdiscus* taxonomy was unresolved, so the extent to which, *e.g.*, growth responses may vary across the multiple species now known in *Gambierdiscus* and *Fukuyoa* genera remains to be clarified. To date, growth data for the following species/phylotypes: *G. australes*, *G. belizeanus*, *G. caribaeus*, *G. carolinianus*, *G. carpenteri*, *G. jejuensis* (formerly known as *Gambierdiscus* sp. type 2), *G. pacificus*, *G. polynesiensis*, *G. scabrosus*, *G. silvae*, *F. ruetzleri*, and *Gambierdiscus* spp. types 3, 4 and 5 can be found in the literature (Chinain et al., 2010a; Kibler et al., 2012; Yoshimatsu et al., 2014; Tawong et al., 2016; Xu et al., 2016; Jang et al., 2018; Vacarizas et al., 2018), and results confirm that differences in both tolerance and optimum growth ranges exist not only across species but strains as well (Vacarizas et al., 2018). Based on sea surface temperature projections over the coming century, a substantial shift in both the distribution and abundance of ciguatera dinoflagellates is to be expected (Parsons et al., 2010; Kibler et al., 2015), with some species becoming dominant whereas others will become less prevalent. In the long-term, however, temperatures may get too warm according to Llewellyn (2010), thereby hindering *Gambierdiscus/Fukuyoa* growth and resulting in a lower risk of ciguatera. In any case, as outlined by Tester et al. (2020): "*as surface waters warm, range extension* (of harmful benthic microalgae) *of several degrees of latitude are anticipated, but only where species-specific habitat requirements can be met (e.g., temperature, suitable substrate, low turbulence, light, salinity, pH)*".

There are very few published data about the influence of pH on the growth and/or toxicity of ciguatera-related organisms. Actually, only one laboratory study has examined the linked effects of pH, temperature and salinity on the cell viability of the marine diatom *Phaeodactylum tricornutum* and has found that low pH combined with high temperature and salinity showed adverse effects on cultures of *P. tricornutum* (Bautista-Chamizo et al., 2018). Concerning the ciguatera-causing dinoflagellates, recent studies on *G. polynesiensis* suggest lower growth rates but increased ciguatoxicity in cultured strains at low pH values (Chinain, unpublished results), which is in marked contrast with data obtained for strains of *G. balechii* and *Gambierdiscus* sp. type 5 which showed a growth suppression at elevated pH, and reduced ciguatoxicity at decreasing pH values (Chan, personal comm.).

Numerous field observations linking climate change to CP outbreaks in the tropical Pacific can be found in the literature: cyclical weather patterns such as El Niño, associated with unusual warming of Pacific Ocean waters, have resulted in spikes of ciguatera cases in the Republic of Kiribati, Western Samoa, the State of Tuvalu and the Cook Islands (Hales et al., 1999), consistent with observations by Gingold et al. (2014) who found an association between CP incidence and warmer sea surface temperatures in the Caribbean basin. A general consensus is that the massive colonization of dead corals by macroalgae provides more substrate for the settlement of epiphytic *Gambierdiscus*/*Fukuyoa* spp. populations (Lewis, 1986; Litaker et al., 2010), as first hypothesized by Randall (1958). This may explain why reef disturbances or degradations linked to extreme climatic events (*e.g.*, hurricanes, heavy rains, coral bleaching) or human activities (*e.g.*, dredging and filling, constructions, military activities) frequently precede ciguatoxic events (Bagnis, 1987; Ruff, 1989; Lehane and Lewis, 2000). In the Cook Islands and French Polynesia, for instance, CP outbreaks were associated with both cyclone activity and infestations of crown-of-thorns starfish (*Acanthaster planci*) (Bagnis et al., 1988; Rongo and van Woesik, 2013; Morin et al., 2016). Similarly, while studying the fluctuations of *G. toxicus* populations in a ciguateric site in Tahiti Island (French Polynesia), Chinain et al. (1999b) found an increase in both the density and frequency of *Gambierdiscus* blooms following unusually high water temperatures, concomitant with a severe coral bleaching episode affecting large areas of the study site. Of note, *Gambierdiscus* spp. cell density peaked approximately 10 months after water temperature started to increase (Chinain et al., 1999b). Further, health impacts (peak number of CP cases) were recorded three months after these peak densities of *Gambierdiscus* (Chateau-Degat et al., 2005), indicating that a time frame of approximately 13 months is required for increased cases of CP to be observed after climate-induced changes to sea water temperature. Such findings substantiate the idea that global warming as a result of climate change may increase the incidence of CP in the South Pacific. Additionally, climate change projections show that the intensity of hurricanes will also increase in the tropical Pacific (Meehl et al., 2007).

2.2.2 Geographical expansion of ciguatera to novel areas: the case study of Rapa Island (Australes archipelago, French Polynesia)

Ciguatera-endemic regions classically overlay coral development areas between 35°N and 35°S, *i.e.*, tropical and sub-tropical areas of the Caribbean Sea, and Pacific and Indian Oceans (Parsons et al., 2012). However, recent observations clearly highlight the current expansion of *Gambierdiscus* spp. and ciguatoxic fish to previously unaffected areas, most notably in temperate locales such as the west coast of Africa (Bienfang et al., 2008) and the eastern Atlantic Ocean (Canary Islands, Madeira, Selvagens Islands) where reports of CP endogenous cases are documented since 2004 (Pérez-Arellano et al., 2005; Boada et al., 2010; Nuñez et al., 2012). These observations are consistent with the concurrent detection of toxigenic *Gambierdiscus* spp. in Macaronesian waters (Fraga et al., 2011; Fraga and Rodríguez, 2014; Pisapia et al., 2017a; Pisapia et al., 2017b; Rodríguez et al., 2017; Reverté et al., 2018), and the confirmation of CTX contamination in locally-sourced fish (Pérez-Arellano et al., 2005; Otero et al., 2010; Caillaud et al., 2012; Bravo et al., 2015; Costa et al., 2018; Estevez et al., 2019; Sanchez-Henao et al., 2019; Sanchez-Henao et al., 2020).

As previously mentioned, similar observations are also documented in the southern hemisphere, such as in New South Wales, Australia (Farrell et al., 2017; Kohli et al., 2017; Seger et al., 2019). The case of Rapa Island (Australes archipelago, French Polynesia) is another emblematic example of the current extension of CP to temperate-like areas of the South Pacific. Rapa Island (27°38'S – 144°20'W) was reputed free of ciguatera until 2008 when six isolated CP cases were first reported (Pawlowiez et al., 2013). Further, from August 2009 to November 2010, a mass-poisoning outbreak involving 114 local residents (based on declared cases, but it is highly likely that half the population was affected) occurred following community fishing in the *rahui* zone, a widely used practice in many PICTs to protect local fishing resources. The unusual severity and magnitude of this outbreak resulted in two fatalities within a three months' period. Clinical records indicated symptoms typical of ciguatera in affected individuals, including cold allodynia, paresthesia and dysesthesia which were reported in 92%, 95% and 86% of affected patients, respectively, at the peak of the epidemic (Tab. 3). Moreover, three fish species were primarily involved in this mass-CP incident, namely *Leptoscarus vaigiensis* (seagrass parrotfish), *Kyphosus cinerascens* (highfin chub) and *Seriola lalandi* (king fish) which were responsible of nearly 90% of the reported cases between 2009 and 2010. Field investigations revealed the presence of toxic *Gambierdiscus* populations in several sampling locations around Rapa Island (Pawlowiez et al., 2013). Additionally, a random test survey of the toxic status of ≈250 herbivorous and carnivorous fish collected from the main fishing sites allowed confirmation of CTXs at concentrations well above the US Food and Drug Administration (FDA) advisory level (0.01 ppb) (US Food and Drug Administration (FDA), 2019) in >60% of the tested fish (Pawlowiez et al., 2013). Fortunately, the local population was highly reactive to educational and community outreach interventions, as illustrated by a five-fold reduction in CP cases between 2009 and 2012 (Fig. 2). Recent data (*i.e.*, mean IR around 128 cases per 10,000 population over the past two years) indicate that ciguatera is still present in Rapa Island but increased awareness among the local population about this toxic threat has helped maintain a low prevalence as compared to the alarming IR peak of 1,758 cases per 10,000 population reported in 2009. A careful analysis of the clinical forms shows that these good results are clearly attributable to self-regulating behavior among the population towards avoidance of high-risk fish species and fishing area, as evidenced by a noticeable shift in the fish species implicated in CP cases over the ensuing years (Fig. 2). Of note, similar encouraging results following public outreach interventions have been previously obtained in Raivavae Island, another ciguatera hotspot in the Australes archipelago (Chinain et al., 2010b). Further investigations are currently underway in order to ascertain the link between this emerging poisoning incident in Rapa Island and global warming in the area (Chinain et al., in preparation).

Tab. 3

Fig. 2

3 Epidemiology of ciguatera poisoning in the Pacific

3.1 The Pacific, a region with the highest ciguatera poisoning incidence rates in the world

Historically, the first description of ciguatera related syndromes in the South Pacific was provided in 1606 by Pedro Fernandes de Queirós (1565–1614) who reported a mass-poisoning event among crew members following the consumption of a snapper in the Republic of Vanuatu. Later, in the 20th century, some Pacific countries such as French Polynesia, New-Caledonia, the Territory of Wallis and Futuna Islands, the Republic of Marshall Islands and the Republic of Kiribati experienced a substantial number of CP outbreaks linked to military activities during and following the World War II (battles, naval ships activities, war material dumping, nuclear test, etc.) (Ruff, 1989; Brunet, 2015).

Based on the South Pacific Epidemiological and Health Information Service (SPEHIS) database (Australian Institute of Marine Science (AIMS), 2009), PICTs are among the nations with the highest IRs in the world as compared to other affected regions of the globe (Lewis, 1984). This was particularly true during the last two decades of the XX's century. Of note, a survey conducted among Marshallese families in 1982, showed that 56% of them counted at least one family member with a previous CP in the past (Lewis, 1984). In Hao Island (French Polynesia), 43% of the inhabitants were affected by CP, two years after the onset of military activities in the atoll (Bagnis, 1969). According to Skinner et al. (2011), it is estimated that ≈ 500,000 people from 17 PICTs where affected by CP over a period of 35 years, with 39,677 CP cases recorded between 1998 and 2008. This corresponds to an annual IR of 194/100,000 people, and represents a 60% increase compared to the IR of 104/100,000 recorded for the period 1973–1983. Based on more recent data, the Republic of Fiji, French Polynesia, the Republic of Kiribati, Queensland (Australia), the Republic of the Marshall Islands, the Cook Islands, Hawaii and the Territory of Wallis and Futuna Islands (where CP was not considered as a concern until 2010), cumulated over 31,461 cases between 2000 and 2016 (Institut Louis Malardé (ILM), 2007-2018; Chateau-Degat et al., 2009; Skinner et al., 2011; Capelle and Lemari, 2015; Skinner, 2015; Iorangi and Nanai, 2017; Disease Outbreak Control Division - State of Hawaii, 2019; Stafford, 2019). It should be noted that the toxic status in a given country/island may significantly vary from one year to another, as illustrated by the example of Rapa Island (French Polynesia) where IRs went from 1,230/100,000 in 2008 up to 17,580/100,000 people in 2009 (Institut Louis Malardé (ILM), 2007-2018). Likewise, since the

80's, IRs reported from several South Pacific countries such as the Republic of Kiribati, the State of Tuvalu, the Tokelau Islands and the Cook islands may sporadically exceed 1,000/100,000 people (Australian Institute of Marine Science (AIMS), 2009). This situation is all the more worrying since it is recognized that CP cases reported in the Pacific likely represent only 20% of the actual cases (Skinner et al., 2011).

Over the past two decades, however, a significant decrease in data collection is observed in the Pacific due to a progressive decline in the documentation of CP incidents in the SPEHIS database by participating countries. To date, fragmented CP data exist for the Oceania region (Goater et al., 2011) with only four countries which currently have specific records of CP cases: (i) the Republic of Fiji, where CP is currently considered as a "high priority" by health authorities (http://www.health.gov.fj/); (ii) French Polynesia, where specific CP epidemiological surveillance tools and strategies are implemented since 2007 (see section 3.2); (iii) Hawaii (Hawaii State Department of Health, https://health.hawaii.gov/docd/disease_listing/ciguatera/); and (iv) Australia, where a "National Ciguatera Fish Poisoning Research Strategy" has been recently launched with the objective of reducing CP incidence through improved risk management (Seger et al., 2019)

The high IRs consistently reported in the Oceania region largely result from the strong reliance of local communities on marine resources (Dalzell and Adams, 1996; Bell et al., 2009; Chinain et al., 2010b; Chan et al., 2011; Rongo and van Woesik, 2011; Kronen et al., 2012). Indeed, in these developing countries, fish consumption rates are among the highest in the world due to limited range of crops and animal protein, with an average annual fish consumption rate between 10.2 – 167 kg/capita/year in PICTs (Bell et al., 2009; Rongo and van Woesik, 2012) vs. a global rate of 18.8 kg/capita/year in 2011, 25 kg/capita/year in Europe, and 7 kg/capita/year in the US (Food and Agricultural Organization of the United Nations (FAO), 2012). There is also a strong tradition of eating fresh fish in PICTs, with 30–90% of the fish caught by the household (Bell et al., 2009; Kronen et al., 2012; Rongo and van Woesik, 2012). But despite these alarming statistics, ciguatera is still largely ignored by most PICT national governments, mostly due to a lack of resources that are dedicated primarily to the control of non-communicable diseases which represent an unprecedented public health issue in the region.

3.2 Survey networks in the Pacific: the example of French Polynesia

French Polynesia (276,300 inhabitants), is composed of 121 high islands and atolls stretching from 134°W to 155°W and 8°S to 28°S (Institut de la Statistique de Polynésie française (ISPF), 2018). Although it has been suggested that the celebrated Polynesian voyages noted from AD 1000 to 1450 in eastern Polynesia may have been prompted by CP (Rongo et al., 2009), the earliest account of CP in French Polynesian dates back to the 18th century and was provided by James Morrison, leading rate on board the *HMS Bounty*, while mooring in the Society archipelago (Jaunez, 1966; as cited in Chinain, 2017). Later, in the 19th century, accounts of the presence of poisonous fish in the Tuamotu, the Gambier and the Marquesas archipelagoes were successively provided by the explorer Jacques-Antoine

Moerenhout, Father Honoré Laval and Father Pierre, respectively (Chinain, 2017). French Polynesia is also the site of nearly five decades of research on ciguatera : following a major poisoning outbreak in Bora Bora Island in 1964 which resulted in three fatalities (Bagnis, 1967), a dedicated ciguatera research unit was created in 1967 at the Institut Louis Malardé (ILM) to investigate the etiology of this enigmatic poisoning (www.ilm.pf). This initiative eventually led to the identification of the causative agent almost a decade later, the dinoflagellate *Gambierdiscus toxicus*, named after the Gambier Island where it was first described (Yasumoto et al., 1977; Bagnis et al., 1980).

In a recent survey conducted on Moorea Island (Society archipelago, French Polynesia), over 50% of households interviewed declared they consume fish six to seven times a week, with 76% of them having at least one member of the household actively involved in local reef fishing activity (Rassweiler et al., 2020). This heavy dependence on fish resources for subsistence explains why French Polynesian communities are so highly exposed to CP risk: between 1999 and 2005, CP was responsible for 96% of hospitalized cases registered under the codification T61: ''*Toxic effect of noxious substances eaten as seafood*'' (International Statistical Classification of Diseases and Related Health Problem (ICD-10) of the World Health Organization) (Gatti et al., 2008). Since 2007, CP annual IRs have varied from 75 to 233 cases/100,000 people (*i.e.*, 202 to 615 cases reported annually), but this number has sporadically reached 17,580/100,000 people in 2009 (Institut Louis Malardé (ILM), 2009). Moreover, no archipelago is spared from ciguatera, from the extreme north of the territory that is subject to a tropical climate, to the extreme south exposed to a subtropical climate. The general trend presently observed in French Polynesia as a whole points towards a stable annual IR, although rates can significantly differ between islands and, in a given island, from one year to another (www.ciguatera.pf).

3.2.1 Since 2007, a country-wide epidemiological surveillance program

Despite the high IRs recorded over the past decades in French Polynesia, CP is not a notifiable disease due mainly to the (too) high prevalence of this illness, the absence of a duly validated laboratory diagnosis for clinical cases and the lack of a clearly defined medical protocol for patient's management (Direction de la Santé de Polynésie française (DSP), 2019). The first CP epidemiological studies in French Polynesia date back to the 1960's (Bagnis, 1967; Bagnis, 1968; Bagnis, 1969). From then, epidemiological data were periodically updated through specific studies (Bagnis et al., 1985; Chateau-Degat et al., 2007a) until 2007 when local health authorities agreed to set up a CP dedicated epidemiological surveillance program jointly managed by the Health Monitoring Office (Public Health Directorate of French Polynesia) and the Laboratory of Marine Biotoxins (LBM) of ILM. Initially, the aim of this program was to take advantage of the existing sentinel network of public health physicians to collect declaration forms filled in by each patient suspected of having CP. Over the years, this network progressively extended to the healthcare workers of the 61 public health medical facilities in French Polynesia (including outlying hospitals, medical centers, dispensaries and infirmaries), and even to some private practitioners. Information gathered on this one-page declaration form, which was updated twice since 2007, concern the patient's age, gender and island of residence, the context of the poisoning (date, fishing area, fish species), the symptoms, the number of previous CP, etc. (Fig. 3). Data collected through this country-wide surveillance program are centralized at LBM-ILM which produces an annual report widely disseminated through the Public Health Directorate website, medical newsletters/forum, social media, local media, etc. In addition, a dedicated email address was created to answer to the general public's questions about CP (veille.ciguatera@ilm.pf).

Fig. 3

Since reporting is made on a voluntary basis, CP prevalence is significantly underestimated throughout the country, especially as many patients tend to forgo medical treatment and/or rely on traditional medicine (see section 4.2.2). It is estimated that ciguatera figures in French Polynesia could quite possibly be at least doubled as, in more than half the reported cases, patients stated they had shared the toxic meal with others at table who had also gone ill but failed to report the poisoning (Chinain et al., 2016). This situation has prompted the implementation of a dedicated ciguatera website (www.ciguatera.pf) in 2014, in an effort to open up the notification program to private practitioners and the general public. The implementation of this community-based participatory reporting program has allowed the production of dynamic risk maps of French Polynesian lagoons, as well as a list of fish species involved in CP incidents in each reporting island. In an effort to increase community outreach, this website also provides a wealth of general information on ciguatera to web users. One main advantage of this IT-based surveillance program is that alerts about the toxic events as well as prevention messages can be issued quickly, since the majority of CP cases are generally notified within 72h after the poisoning incident.

In case of a major outbreak, the response mechanism to CP incidents currently in place in French Polynesia involves three main entities, each having specific mandates: (i) the Health Monitoring Office which issues CP outbreak alerts; (ii) the Hygiene and Public Health Department which sends requests for confirmatory analyses on suspect fish batches and takes all necessary measures to remove toxic fish from retail outlets; and (iii) the LBM-ILM, in charge of conducting confirmatory analyses on suspect fish samples, and field campaigns to investigate the etiology of mass-poisoning outbreaks in newly affected areas.

3.2.2 Contribution of herbivores and marine invertebrates to ciguatera poisoning incidents

According to Halstead (1978), more than 400 fish species are considered to be potential vectors of CP. Historically, CP was thought of as a "carnivore problem" (Lewis, 2006; Rongo and van Woesik, 2011), and in fact, Serranidae, Lutjanidae, Carangidae, Muraenidae, Lethrinidae, Sphyraenidae consistently account for the majority of outbreaks worldwide

(Quod and Turquet, 1996; Oshiro et al., 2010; Caillaud et al., 2012; Tester et al., 2013; Chan, 2015b; Hossen et al., 2015; Farrell et al., 2017). However, it is well established that the transfer of algal CTXs in the food web requires passage through herbivorous fish (Lewis and Holmes, 1993). This may explain why in CP-prone reef ecosystems, clear shifts in the types of reef fishes involved in CP were generally observed beginning with herbivores, then followed by carnivores years later (Bagnis et al., 1988; Rongo and van Woesik, 2011).

(a) Herbivorous fish species are major contributors to ciguatera poisoning events in French Polynesia

Unlike what is observed in other CP endemic areas such as the Indian Ocean, the Caribbean and the eastern Atlantic Ocean where CP events rarely involve herbivorous species, in the Pacific, Scaridae, Acanthuridae and Kyphosidae are frequently reported in CP cases occurring in the Cook Islands (Rongo and van Woesik, 2011) and French Polynesia (Darius et al., 2007; Chinain et al., 2010b; Pawlowiez et al., 2013). Of note, from 2008 to 2018, herbivorous species consistently ranked among the top 5 species most frequently involved in CP cases recorded annually in French Polynesia (www.ciguatera.pf), accounting for approximately 14 to 33.6% of cases. Table 4 compares the CTX contents found in herbivorous, omnivorous and carnivorous species (either fish or marine invertebrates) in three Pacific islands: Raivavae (Australes archipelago, French Polynesia), Nuku Hiva (Marquesas archipelago, French Polynesia) and Marakei (Republic of Kiribati). Results confirm that these three islands should be regarded as ciguatera hotspots as significant levels of CTXs were detected in all trophic levels of the food web (Tab. 4). Another important finding is that, in some cases, the amounts of CTXs found in herbivorous species can largely exceed those measured in carnivores, although the highest concentration, *i.e.*, 81.84 ppb P-CTX1, was found in top apex predator such as Muraenidae (Tab. 4). When different tissues (*e.g.*, flesh vs. liver) were compared for their toxicity in Mureanidae specimens, data showed the liver generally harbored higher toxin concentrations (Chan et al., 2011; Jiang et al., 2012) as reported elsewhere in the literature (Arnett and Lim, 2007; O'Toole et al., 2012; Kohli et al., 2017; Clausing et al., 2018) (Tab. 4). Fortunately, these fish are rarely consumed by local populations due to their bad reputation.

Tab. 4

Based on detailed LC-MC/MS studies by Yogi et al. (Yogi et al., 2011; Yogi et al., 2014), distinct regional differences and species-specific toxin profiles in fish may explain the regional variations observed in fish toxicity. Therefore, gaining insights into the CTX profiles of CP-prone fish species is useful to inform risk assessment and management programs. Studies conducted on three species frequently involved in CP incidents in French Polynesia, *i.e.*, *Chlorurus microrhinos* (ex *Scarus gibbus*, steephead parrotfish), *Lutjanus bohar* (red snapper) and *Gymnothorax javanicus* (giant moray eel) confirmed the remarkable diversity encountered in the toxic profiles of fish from various trophic levels of the ciguatera food chain (Murata et al., 1989; Legrand et al., 1990; Murata et al., 1990; Satake et al., 1998) (Fig.

4), consistent with observations by Mak et al. (2013) collected from various species representative of distinct trophic levels in the Republic of Kiribati.

Fig. 4

(b) Marine invertebrates as novel vectors of ciguatera poisoning in French Polynesia

Ciguatera classically results from the ingestion of tropical and subtropical coral reef fish. However, the epidemiological surveillance program in French Polynesia allowed to highlight that a variety of marine invertebrates, which also represent a valuable source of protein and revenue for Pacific islands communities, may occasionally be involved in CP-like incidents.

The first report concerns the giant clam *Tridacna maxima* which was implicated in a mass-poisoning event in 1964 in Bora Bora Island (Society archipelago) leading to three fatalities (Bagnis, 1967). Years later, from 2001 and onwards, similar incidents were again reported from French Polynesia, but also New Caledonia, the Republic of Vanuatu and the Cook Islands (Laurent et al., 2008; Rongo and van Woesik, 2011; Laurent et al., 2012). Of note, besides the digestive and neurological manifestations typically evocative of a CP, patients displayed additional symptoms, such as the rapid onset of the disease, burning of mouth and tongue, and unusual severity of symptoms including paralysis in some patients which require their hospitalization (Laurent et al., 2012).

Additional poisoning cases following the ingestion of sea urchins, *i.e.*, *Tripneustes gratilla*, have also been described in French Polynesia in 1958 (Randall, 1958) and in 2005 (Pawlowiez et al., 2013). In this latter study, fractionation experiments of toxic extracts by high performance liquid chromatography (HPLC) bio-guided with CBA-N2a and rRBA suggested the presence of CTX-like compounds in sea urchins from Rurutu Island (Pawlowiez et al., 2013). Toxic incidents following the ingestion of *Tripneustes gratilla* and *Tectus niloticus* (gastropod) were subsequently reported in 2014 and 2015 from Nuku Hiva Island (Marquesas archipelago) (Darius et al., 2018a; Darius et al., 2018b). Patients experienced both classic and atypical symptoms (Gatti et al., 2018b), as the one previously reported by Laurent et al. (2012). Coincidentally, the affected area in Nuku Hiva Island was also the one with high *Gambierdiscus* densities and high prevalence of toxic fish (Darius et al., 2018a; Darius et al., 2018b).

Detailed toxicological analysis using the CBA-N2a and LC-MS/MS were further performed on *T. niloticus* and *T. gratilla* toxic samples collected from Anaho Bay, a long-standing ciguatera hotspot from Nuku Hiva Island (https://www.ciguatera.pf/index.php/fr/nos-services/bilan-annuel). They allowed for the unambiguous detection of CTX compounds in these samples (Darius et al., 2018a; Darius et al., 2018b), at levels consistently above the guidance level of 0.01 ng of P-CTXs per gram of fish flesh (or 0.01 ppb) recommended by the European Union and US Food and Drug Administration (European Food Safety Authority (EFSA), 2010; US Food and Drug Administration (FDA), 2019). Based on LC-MS/MS data, at least five distinct CTX congeners could be detected (Darius et al., 2018a; Darius et al., 2018b), some of which are known to be primarily produced by *G. polynesiensis* in *in vitro* cultures (Chinain et al., 2010a; Longo et al., 2019) (Fig. 5). Interestingly, some of these compounds also corresponded to the CTXs mainly detected in giant clams (*T. maxima*) experimentally fed highly toxic cells of *G. polynesiensis* (Roué et al., 2016; Roué et al., 2018b). All these findings suggest that *Gambierdiscus* is the likely source of the CTX compounds naturally bio-accumulated in a variety of marine invertebrates.

Fig. 5

It should be noted that reports of sporadic emerging or re-emerging poisoning cases following the consumption of popular marine invertebrates not only concern French Polynesia. At a regional scale, *T. maxima*, *Octopus cyanea* (big blue octopus), *Percnon* spp. (nimble spray crab) and *Dendropoma maxima* (large worm shell) from the Cook Islands were reportedly implicated in CP incidents (Rongo and van Woesik, 2011), as well as *Panulirus penicillatus* (lobsters) and octopus in the Republic of Kiribati (Mak et al., 2013).

3.2.3 Confirmatory analyses in fish remnants

CP is diagnosed clinically when characteristic symptoms follow the ingestion of ciguatera-prone marine products. However, one way of confirming the diagnosis of ciguatera is by testing food remnants for the presence of CTXs. As previously mentioned, the amount of CTXs considered to be harmful for human consumption is estimated at 0.01 ppb, taking into account a 10-fold safety margin (European Food Safety Authority (EFSA), 2010; US Food and Drug Administration (FDA), 2019).

Toxicological investigations aiming at linking the amount of CTXs found in toxic meal remnants to patients' clinical symptoms were conducted as part of the surveillance program currently in place in French Polynesia. Tab. 5 details the CTX contents measured by means of rRBA in fish remnants involved in CP cases in 15 French Polynesian patients. Results showed that CTXs varied from 0.38 to 8.38 ng P-CTX3C eqv.g^{-1} (or 0.16 to 3.51 ng P-CTX1B eqv.g^{-1}), consistent with the risk value of 0.1 ng P-CTX1B eqv.g^{-1} of fish flesh proposed by Lewis (Lewis, 2001). Interestingly, the variety (number) of symptoms recorded does not seem to be linked to the CTX concentration in fish leftovers (Tab. 5). These findings are in good agreement with LC-MS/MS data obtained from fish implicated in local CP incidents in Australia, showing P-CTXs contents ranging from 0.02 to 14.9 ng P-CTX eqv.g^{-1} in fish (Hamilton et al., 2010; Farrell et al., 2016; Farrell et al., 2017; Edwards et al., 2019). As in French Polynesia, these data exclusively concerned carnivorous species such as the Spanish mackerel (*Scomberomorus commerson*), redthroat emperor, purple rockcod, green jobfish grouper and sawtooth barracuda.

Tab. 5

The very high levels of CTXs found in fish from the Pacific raise the question of the potential effects of CTX accumulation in fish. CTXs are known to bind to both sodium channels isolated from mammalian (rat) and fish brains, therefore a high toxin load is likely to cause morphological changes and/or abnormal behavior in fish (Lehane and Lewis, 2000; Ledreux et al., 2014; Clausing et al., 2018, and references therein). Concentrations of CTXs well above 10 ng.g^{-1} have been detected in Pacific herbivorous species such as *Scarus rubroviolaceus* and *Ctenochaetus striatus* (*i.e.*, 18.04 and 12.65 ng P-CTX3C eqv.g^{-1}) as well as in omnivorous species such as *Crenimugil crenilabis* and *Liza vaigiensis* (*i.e.*, 21.02 and 16.23 ng P-CTX3C eqv.g^{-1}, respectively) (Darius et al., 2007), with no apparent detrimental effects on their behavior and/or physiology. Similar observations exist for carnivores such as *Cephalopholis argus* and moray eels, with concentrations ranging from [10–24.4] ng P-CTX1B eqv.g^{-1} and [17.17–81.8] ng P-CTX1B eqv.g^{-1}, respectively (Chan et al., 2011; Bienfang et al., 2012; Jiang et al., 2012; Mak et al., 2013). These data clearly suggest adaptations for resistance in fish or marine invertebrate species naturally exposed to CTXs in the wild (Banner et al., 1963; Clausing et al., 2018).

4 Socio-economic impacts and ciguatera perception in Pacific Island Countries and Territories

Evaluating the true socio-economic impacts of CP on the life of the 400 million people living in tropical and subtropical coastal regions (Glaziou and Legrand, 1994) proves extremely challenging due to its numerous sociological and cultural ramifications that go far beyond the public health aspects. For example, a survey conducted among Rarotonga communities (Cook Islands) showed that CP may interfere and disrupt the intergenerational transmission of traditional knowledge in affected communities, particularly with regard to fishing practices (Rongo and van Woesik, 2012). Too, the potential damage to trade, tourism and indirectly to health by poor nutrition and diet modification following ciguatera outbreaks are also often overlooked. For example, Rongo et al. (2009) draw attention on the shift towards processed foods in the Cook Islands and the 1990s mass migration of Cook Islanders to New Zealand and Australia during CP events. On another plan, assessing the ciguatera perception among local populations in relation with adaptive strategies to avoid or limit their daily exposure to this toxic threat may also prove useful in promoting targeted prevention messages in the frame of risk management programs. As it stands, the secular cohabitation of Pacific islands communities with ciguatera often results in high risk-taking behaviors.

4.1 Socio-economic impacts of ciguatera poisoning, including dietary and cultural shifts

A remarkable effort to evaluate the worldwide economic impact of HABs has been undertaken in 2007 by Nau (2007) as a PhD project. Information compiled from 17 countries revealed a range of annual costs from USD $1,712,784 to USD $185,573,530. Recently, an extensive assessment of the global cost of algal bloom has been conducted, taking into account all aspects including human health impacts, commercial fishery impacts, tourism/recreation impacts, monitoring and management impacts (Sanseverino et al., 2016). Although the ciguatera issue was included in these two studies, it only represented a marginal part of the estimated costs.

On a local and punctual basis however, the cost of medical expenses linked to ciguatera outbreaks *stricto sensu* can be estimated. For example, in the French Polynesian island of Moorea, this cost has been estimated to USD $241,847 over the single time period of 2007–2013 (Morin et al., 2016). In addition, the negative outcomes of CP on the populations of endemic area go way beyond the cost of intoxication cases medical treatment. Instead, CP consequences have huge economic and social impacts for PICTs. First, the threat of CP induces a loss of confidence of consumers towards fish and seafood which are a primary and high nutritional value food resource for these populations, but also their main protein source from a traditional point of view (Dalzell and Adams, 1996; Bell et al., 2009; Kronen et al., 2012). It thus causes a progressive shift of the dietary patterns of locals towards less healthy products resulting in a strong reliance on imported and/or canned products, with the risk of increasing sugar and fat intake (Lewis and Ruff, 1993; Dewailly et al., 2008; Counil et al., 2009; Ferland et al., 2009; Rongo and van Woesik, 2011; Gillett, 2016; Friedman et al., 2017). Socioeconomic consequences of CP have been carefully studied in 2011 on the example of Rarotonga, one of the southern Cook Islands (Rongo and van Woesik, 2011). The authors collected data on protein consumption preferences from 179 households and compared them with a previous similar study. They showed that consumption of fresh fish had been diminished by 50% between 1989 and 2006 due to CP events while alternative proteins (mostly imported meats) had increased. These authors also used a "cost savings-and-avoidance" valuation technique to estimate the direct loss in marketable goods and services value which allowed them to evaluate the economic consequences of CP around NZD $750,000 per year and the approximate costs of dietary shifts to NZD $1 million per year. Hence on one hand the average cost of food rations increases as an indirect consequence of CP, and on the other hand this progressive dietary shift leads to the appearance of health issues such as diabetes, obesity, and cardiovascular troubles directly related to alimentary choices. The increased occurrence of these metabolic diseases in turn significantly raises the public health expenses (Skinner et al., 2011). Additional economic consequences include a decrease in productivity of the exposed populations, of local fishermen incomes as well as exportations opportunities (Magnien, 2001; Bauer et al., 2010; Berdalet et al., 2016; Gillett, 2016). In addition, these costs estimations neither include the expenses of chronic effects care nor the cost of diagnostic difficulties experienced in countries located in temperate areas by the returning tourists who contracted CP during their stay in PICTs. Finally, legal actions can be undertaken by affected consumers against restaurants and/or fish suppliers, a new kind of lawsuits which is expected to only increase in the coming years.

PICTs are already challenged with an array of environmental problems such as land degradation, coastal erosion, loss of terrestrial and marine biodiversity, contamination of freshwater resources due to urban, agricultural and industrial development and marine pollution and coral reef degradation (Barnett, 2011). PICTs ecosystems are thus considered as extremely vulnerable to the effects of climate change. Given the critical role of fisheries in their food supply and economic development the potential consequences of climate change on food security is especially threatening for these communities (Gillett, 2016). Indeed, the United Nations Food and Agriculture Organization (FAO) predicts ciguatera to become an increasing food safety threat due to climate change at a global scale (Food and Agricultural Organization of the United Nations (FAO), 2014). Should this prediction prove to be accurate, the economic and social burden of ciguatera will rise exponentially with both climate change and world trade globalization. Hence, a smart and thorough planning of the use of fish for food security in the Pacific regions should be conducted to avoid potentially dramatic lack of this essential resource before 2030 (Bell et al., 2009). Collaboration between the governments of all concerned countries and territories is required to develop multiple solutions, such as increasing local access to tuna, develop aquaculture and diversify the fish supply. Concerning aquaculture, three regional organizations, *i.e.*, the Pacific Community (SPC), the International Center for Living Aquatic resources Management (ICLARM) and the University of the South Pacific (USP) have recently committed to a “Regional Strategy for the Development of Aquaculture” which should help decision-making by convening regular meetings of island nations, stakeholders and other local organizations (Adams et al., 2000). However, long-term research and education programs are required to design and test economically and environmentally sustainable methods for expansion of aquaculture in the Pacific region.

4.2 Risk-taking behaviors *vs*. adaptive strategies among island communities

Based on data collected through the epidemiological surveillance program currently established in French Polynesia, approximately 52% of patients affected by CP in 2018 has actually experienced a previous CP at least once in their lifetime (over 10 to 20 times for some patients) (Institut Louis Malardé (ILM), 2007-2018). This was particularly visible in communities living in the most remote islands of French Polynesia where food availability and diversity is more limited than in Tahiti and the main islands (Gatti et al., 2018a). These data are consistent with the results of a study conducted in 2005 in New Caledonia among 559 patients, which indicated that 37.8% already presented a history of CP (Baumann et al., 2010), as well as observations by Rongo and van Woesik (2011) in the Cook Islands.

In some atolls of the Tuamotu archipelagoe, with limited food supply and high unemployment, the population has no other choice than to eat the product of their daily fishing, even if they are aware of a potential toxic hazard. In a recent questionnaire survey conducted in Takaroa, Raivavae and Mangareva Islands, 29% of informants with a previous history of CP declared they were fully aware they were taking a risk to get poisoned. Among the many reasons given for this high risk-taking behavior were: (i) they suspected the fish was toxic but deliberately consumed it to prevent other family members from poisoning themselves; (ii) the pleasure of eating the fish (even toxic) was more compelling than the “inconvenience” associated with CP (ILM, unpublished data). Another possible explanation for this somewhat fatalistic attitude may be the strong confidence local populations have towards a number of traditional remedies that are easily accessible to everyone (see section 4.2.2).

4.2.1 Adaptive strategies developed by local populations in French Polynesia to limit ciguatera poisoning risk

Toxic fish are not distinguishable from edible ones as CTXs do not seem to affect fish physiology and behavior, fish aspect (skin color variation), smell or taste (Lehane and Lewis, 2000). Of note, CTXs are present in fish in trace levels (nanograms) making their detection very challenging. Therefore, in the absence of field test kits readily available for local people and fishermen, local populations have no other way out but the use of ancestral folk tests to detect toxic individuals (Lewis, 1983; Alvarez et al., 1990).

One frequent way to struggle for life in many communities in PICTs was the oral transmission of folk knowledge from one generation to the next. Despite the risks of loss related to oral tradition, popular beliefs in PICTs have maintained the knowledge about several folk detection tests to avoid ciguatera (Darius et al., 2013). To date, a wide range of tests are still largely used: *e.g.,* feeding ants or flies with a small piece of fish; cooking fish with a silver coin or ring and looking for skin discoloration; watching for the physical aspect of the flesh (Lewis, 1983; Lewis, 1986; Chinain et al., 2010b; Darius et al., 2013). The most widespread test, however, is a simple “folk bioassay” which consists in feeding a piece of fish (usually the liver) to a dog or a cat, and watch for signs of poisoning in the animal (Lewis, 1983; Lewis, 1986; Darius et al., 2013). If most of these tests are frequently mentioned in the literature, none of them have been scientifically evaluated for their effectiveness. For instance, the “folk bioassay” itself can hardly be evaluated even in laboratory conditions, for obvious ethical reasons (Lewis, 1987; Dickey and Plakas, 2010).

A study aiming at evaluating the effectiveness of two traditional methods, namely the *rigor mortis* test (RMT) and the hemorrhagic test (HT), was conducted in Raivavae Island (Australes archipelago). Based on RMT and HT, flabby fish or the presence of hemorrhagic signs at the tail of the dead fish, respectively, are the signs that these individuals are toxic ones (Darius et al., 2013). A total of 107 fish collected by spear-fishing at various fishing sites around the island were further subjected to the diagnosis of five local testers by means of these two tests, and the results compared with laboratory toxicity data obtained via the rRBA (Darius et al., 2013). Results showed that the performance of RMT and HT varied from one tester to another, depending primarily on the tester’s skillness and/or whether he had a long practice of the test. The best scores observed were 55% and 70% respectively for RMT and HT. The best agreement between testers was also obtained with HT. Moreover, results also suggested that the best way to limit the number of poisoning cases would be to perform the RMT and HT in parallel (Darius et al., 2013). It was concluded that the use of these two traditional tests combined with a good knowledge of the risky fishing zones and fish species may help reduce CP in areas where CP is endemic. Another obvious advantage of these homemade tests is that they can be carried out on the fishing site itself at a lower cost, and therefore may constitute undeniable assets in terms of ciguatera risk management on a daily basis.

Complementary to these folk detection tests, local populations have also developed a number of adaptive strategies to avoid or limit the risk of contracting CP: *e.g*. reject risky fish species, avoid risky fishing areas, discard liver and head, preferentially eat fish specimens of smaller size for a given species, space out fish meals, etc. (Lewis, 1983; Lewis, 1986). However, the research progress achieved in the past decades have led to progressively reconsider several of the early paradigms or common assumptions in ciguatera, in particular those pertaining to factors likely to influence toxins concentration in fish. For example, studies aiming at examining the relationship between toxicity and fish size or weight exist for a limited number of species. While some authors concluded that biological characteristics such as size, weight or lipid content were not a good predictor of fish ciguatoxicity (Pottier et al., 2002; Darius et al., 2007; Dierking and Campora, 2009; Chinain et al., 2010b; Bienfang et al., 2012; Caillaud et al., 2012; Darius et al., 2013; Mak et al., 2013; Gaboriau et al., 2014; Robertson et al., 2014; Bravo et al., 2015; Soliño et al., 2015; Kohli et al., 2017), others reached contradictory conclusions (Oshiro et al., 2010; Chan et al., 2011; Wong et al., 2014; Ha et al., 2018; Loeffler et al., 2018). Such findings suggest that CTX concentration in fish tissues may be the result of more complex biological and physiological processes. Moreover, although size is very useful to describe the morphology of a fish, it does not provide accurate information on its age, its past growth trajectory and its physiological state, as some fish species will reach their maximum size at a very young age, while in other species the maximum size will be reached only after several years (Nadon et al., 2015). In this regard, an estimate of the real age of fish via the analysis of otoliths of fish appears much more relevant (Campana and Thorrold, 2001; Vigliola and Meekan, 2009) and could prove useful to inform fish toxicity predictive models. In conclusion, current management practices based on the simple avoidance of fish of certain sizes (Clua et al., 2011; Sumner et al., 2011; Sydney Fish Market, 2013; Chan, 2015b; Chan, 2015a; Sanchez-Henao et al., 2019) do not seem of much use to the consumers to minimize CP risk, but may cause significant financial losses to the fishing industry instead.

4.2.2 Use of traditional remedies to treat ciguatera

Allopathic medicine has as yet failed to develop a truly effective and specific treatment for ciguatera and consists mainly of a symptom-based palliative approach (Friedman et al., 2017). Alternatively, many South Pacific communities use traditional remedies to treat ciguatera, especially in remote locations where limited healthcare services are available. Ethnobotanical research conducted by the Institut de Recherche pour le Développement (IRD) among Pacific islands communities have identified nearly 100 plants of interest used in traditional medicine for ciguatera treatment or prevention (Bourdy et al., 1992; Laurent et al., 1993). Roots, leaves, bark or fruits are prepared by decoction, infusion or maceration, in different proportions and to a proper dosage, based on “recipes” transmitted from one generation to the next (Bourdy et al., 1992; Laurent et al., 1993; Kumar-Roiné et al., 2011).

French Polynesia does not stand as an exception in the Pacific region as an important traditional healers community is established in this country, which can locally represents more than a dozen of healers for less than 600 inhabitants, as reported by Moretti et al. (2015) in Fatu Hiva island (Marquesas archipelago). Moreover, a survey conducted among 88 public healthcare professionals exercising in French Polynesia in 2018, revealed that 49% of them were keen to recommend the use of traditional medicine to CP patients, especially the one prepared from the leaves of *Heliotropium foerterianum* (or *tāhinu* in local language) (Tranchet et al., 2018). Of note, in certain locales of the Tuamotu archipelago where *H. foerterianum* is widely present and accessible to everyone, local residents have so much confidence in the effectiveness of this traditional remedy that they no longer fear CP episodes (ILM, 2019, unpublished data).

The potential presence of active molecules capable of counteracting the neurotoxic effects of CTXs was sought in the extracts of ≈ 20 plants using CBA-N2a (Boydron-Le Garrec et al., 2005; Kumar-Roiné et al., 2009) and rRBA (Kumar-Roiné et al., 2009). Only extracts prepared from the roots of *Pandanus tectorius* and leaves of *Vitex trifolia* and *H. foertherianum* showed an ability to inhibit the binding of CTXs on site 5 of VGSCs (Kumar-Roiné et al., 2009). These results were consistent with a previous study showing the ability of *H. foertherianum* extracts to inhibit spontaneous and repetitive discharges of the action potential as well as the swelling observed at the level of the frog myelinated axons induced by P-CTX1B (Benoit et al., 2000). Bio-guided fractionation carried out on leaf extracts of *H. foertherianum* further led to the formal identification of its main active principle, *i.e.*, rosmarinic acid (RA), a compound widely known for its numerous biological properties (antioxidant, anti-inflammatory, bactericidal, fungicidal, and beneficial effects on the cardiovascular system and neurodegenerative diseases) (Kumar-Roiné et al., 2009).

Subsequent studies compared the effects of RA *vs*. a leaf decoction of *tāhinu* on the viability of neuroblastoma cells exposed to P-CTX1B, and allowed to confirm the beneficial effects of both extracts although the traditional remedy proved five-fold more active than RA alone, which suggests a possible synergistic action of the 24 co-occurring compounds identified in the extract of *tāhinu* leaves and whose chemical structures remain to be elucidated (Rossi et al., 2012). The neuroprotective effects of RA on P-CTX1B in primary human neurons was also demonstrated by Braidy et al. (2014). It should be noted that a great variability in RA contents is observed from one site to another, certainly influenced by environmental factors but also by the composition of the soil or exposure to the sun and winds (Rossi, 2014). This spatial variability in RA contents could partly explain why the effectiveness of the remedy varies between islands/archipelago.

In summary, although no clinical trial has been carried out to duly validate the effectiveness of this traditional remedy at a large scale, results already available clearly highlight the potential that exists around the *tāhinu* leaves traditional remedy. Further research efforts should examine the possibility of making concentrates of *H. foertherianum* commercially available in the form of infusion bags pre-dosed with active ingredients. In any case, this traditional remedy offers a promising alternative to symptomatic (palliative) treatment generally regarded as ineffective by most patients. However, to be effective, this remedy must be taken very quickly, *i.e.*, within hours after the onset of clinical symptoms. Combined with early diagnosis of the disease, it may significantly help reduce the risk of developing chronic forms in ciguateric patients.

5. Risk assessment and management of ciguatera in the Pacific

The implementation of risk assessment and management programs in every PICT highly exposed to CP risk, should be regarded as a public health priority in the Pacific region. But to ensure sustainable results, any defined action plan should be considerate of the limited resources generally dedicated to the mitigation of this toxic threat by PICT national governments. This section will examine several management options readily implementable in PICTs, including: (i) the deployment on a routine basis of easy-to-use, low-cost field-monitoring devices to allow provision of timely advise on locations at risk of ciguatera; (ii) the selection of specific laboratory toxin detection tests well adapted to the context of ciguatera in PICTs (*e.g.,* high endemicity); and (iii) the choice of appropriate communication and outreach strategies for increased awareness about ciguatera among local communities.

5.1 Detection tools

5.1.1 *Gambierdiscus polynesiensis* as a potential biomarker of ciguatera poisoning risk?

Management of CP is difficult, because its occurrence in reef ecosystems is generally associated with complex assemblages of multiple *Gambierdiscus/Fukuyoa* species characterized by highly divergent toxicities according to the suite of CTX congeners they produce, in addition to the amount (Yogi et al., 2014; Darius et al., 2018b). Gaining insights into the diversity and relative abundance of the different species of *Gambierdiscus*/*Fukuyoa* spp. present in a given locale can thus inform ciguatera hazard maps in CP-prone areas (Smith et al., 2017; Darius et al., 2018b; Rhodes et al., 2020), provided sampling designs properly address the issues of potential patchy distribution and/or substrate preferences and seasonal variations in cell abundance (Parsons et al., 2012, for reviews and references therein; Chinain et al., 2020).

It is believed that the ciguatoxicity in a given area depends primarily on the presence of selected highly toxic species of *Gambierdiscus* that may not be the numerically dominant species but which contribute disproportionately to the overall flux of CTXs in the environment (Litaker et al., 2010; Longo et al., 2019). A vast majority of the *Gambierdiscus* and *Fukuyoa* species/strains identified as likely producers of CTXs or CTX-like compounds, actually exhibit very low toxicity, ranging from several femtograms to sub-picograms per cell (Chinain et al., 2020, for a review and references therein). Only two species proved significantly more toxic than the others, producing pg amounts of CTXs: *G. polynesiensis* (Chinain et al., 2010a; Rhodes et al., 2014; Longo et al., 2019) and *G. excentricus* (Fraga et al., 2011; Litaker et al., 2017; Pisapia et al., 2017a), which are therefore recognized as important contributors to CP in the South Pacific and the Atlantic Oceans, respectively. Recent findings suggest that *G. silvae* possibly fill that role in the Caribbean region (Robertson et al., 2018).

As an example, published toxicity records for *G. polynesiensis* range from 1.2 up to 18.2 pg.cell^{-1}, as determined by various analytical methods (Chinain et al., 2010a; Rhodes et al., 2014; Roué et al., 2016; Darius et al., 2018b; Longo et al., 2019). Of note, this species, which is currently only known from the Pacific Ocean, has been consistently described from locations reputed at high risk of ciguatera (Skinner et al., 2011), such as French Polynesia (Darius et al., 2018b; Longo et al., 2019), the Cook Islands (Rhodes et al., 2014) and the Kingdom of Tonga (Smith et al., 2017). Therefore, the species *G. polynesiensis* may reasonable serve as a biomarker of elevated CP risk in routine cell-based risk assessment programs, as recently demonstrated in a historical ciguatera hotspot of Nuku Hiva Island (Marquesas archipelago, French Polynesia) (Darius et al., 2018b) (see section 5.1.2). However, one cannot exclude that other species with lower ciguatoxicity but wide geographical distribution can significantly contribute to the bioaccumulation of CTXs in marine food webs as well, as is the case for the species most frequently noted in the literature, *i.e.*, *G. australes* (Rhodes et al., 2020). Indeed, toxicity data currently available for this species clearly highlight a generally low CTX-like activity but the ability of certain strains to produce copious amounts of other ciguatera-related metabolites, such as MTXs congeners and two compounds in the gambierone group (Chinain et al., 1999a; Chinain et al., 2010a; Nishimura et al., 2013; Rhodes et al., 2014; Lewis et al., 2016; Munday et al., 2017; Pisapia et al., 2017a; Rhodes et al., 2017b). Although MTXs are generally considered of lesser concern for CP than CTXs because of their low tendency to accumulate in fish flesh (Yasumoto et al., 1976), their possible role in CP cannot be disregarded as eating non-eviscerated fish is a common practice in many PICTs (Chateau-Degat et al., 2007b). Moreover, recent studies have provided evidence that gambierones may share similar biological activities with CTXs, although with much less potency (Rodríguez et al., 2015; Boente-Juncal et al., 2019). All these findings warrant further investigations to clarify the exact role of these compounds in CP, including their mode of action and targets in mammalian cells.

5.1.2 Field-monitoring tools

Monitoring *Gambierdiscus*/*Fukuyoa* cell abundance in the environment is useful to inform CP risk assessment and management programs (Litaker et al., 2010) as CP outbreaks are traditionally linked to blooms of these dinoflagellates. Such surveys are commonly based on the sampling of natural substrates, *i.e.*, macrophytes (Grzebyk et al., 1994; Chinain et al., 1999b; Rhodes et al., 2010; Tester et al., 2013; Díaz-Asencio et al., 2019b). However, the obvious lack of standardization inherent to this method (variations in both cell densities across macroalgal hosts and substrate availability across sites and seasons) (Bomber, 1985; Lobel et al., 1988) led researchers to explore the use of artificial substrates for the monitoring of various ciguatera-related benthic HAB species, including *Gambierdiscus*/*Fukuyoa* spp., *Ostreopsis* spp. and *Prorocentrum* spp. (Kibler et al., 2010; Tester et al., 2014). These artificial substrates generally consist of fiberglass window-screens (WS) floating freely above the sediment and deployed in the environment for 24h (Fig. 6A) (Moreira and Tester, 2016). Over the past ten years, this method was tested in a number of studies worldwide which also examined the relevance of using different materials, sizes and deployment times (Tan et al., 2013; Parsons et al., 2017; Ho and Bing, 2018; Yong et al., 2018; Fernández-Zabala et al., 2019; González et al., 2019). This technique offers multiple advantages: it is user-friendly (devices can be easily deployed almost anywhere), cost-effective and samples can be further analyzed by means of molecular identification techniques such as quantitative Polymerase Chain Reaction (qPCR) (Vandersea et al., 2012; Nishimura et al., 2016; Kretzschmar et al., 2019b; Litaker et al., 2019), Restriction Fragment Length Polymorphisms analysis (Lyu et al., 2017), or high-throughput sequencing (Sassenhagen and Erdner, 2017; Smith et al., 2017) to obtain information on the diversity and relative abundance of ciguatera-related dinoflagellates in the sampling site. This information is particularly useful for an accurate evaluation of CP risk in a given location since *Gambierdiscus* and *Fukuyoa* species are known to show differential toxicity (see sections 2.1.2 and 5.1.1). These artificial substrates also provide clean cell samples useful for subsequent isolation and *in vitro* culturing experiments aiming at establishing an algal collection of strains of *Gambierdiscus* spp. most representative of CP hotspots in French Polynesia. Consequently, these devices are now used on a routine basis in risk monitoring programs currently conducted in French Polynesia. In some islands, this technology proved useful in determining some of the factors likely to influence CP risk in a given site, as was the case in Nuku Hiva Island (Marquesas archipelago) where these passive samplers were deployed in three different sites with contrasting CP risk. Species-specific qPCR assays allowed the detection of six species in this island, including *G. australes*, *G. caribaeus*, *G. carpenteri*, *G. pacificus*, *G. polynesiensis* and *G. toxicus* (Darius et al., 2018a; Darius et al., 2018b). Results also revealed that *G. polynesiensis* was the predominant species (82%) in Anaho Bay, a historical ciguatera hotspot, whereas *G. carpenteri* which is known as a low toxin producer for CTXs at a global scale (see section 2.1.2) (Chinain et al., 2020, for a review and references therein) predominated in Taipivai and Taiohae Bays (90%), two spots regarded as at low-risk of CP (Darius et al., 2018b).

In parallel to this cell-based method, an easy-to-use toxin-based method, *i.e.*, the Solid Phase Adsorption Toxin Tracking (SPATT) technology, has continuously gained in popularity since its first introduction in 2004 (MacKenzie et al., 2004). Known for their relatively low cost, SPATT samplers are also very simple to prepare, deploy, transport and store (MacKenzie, 2010). They consist of a filter made of a porous synthetic resin (*e.g.*, Diaion® HP20, so far the most used resin) capable of adsorbing dissolved toxins circulating in the water column, and is deployed in monitored areas for few hours to several days (Fig. 6B) (Kudela, 2017; Roué et al., 2018a, for reviews and references therein). The use of this passive sampling method, coupled with LC-MS/MS analyses performed in a multi-toxin screening format, has demonstrated its ability to detect a large array of lipophilic and hydrophilic toxins produced by various microalgae and cyanobacteria, in both marine and freshwater environments (Kudela, 2017; Roué et al., 2018a, for reviews and references therein). And in fact, this technology has been recently used with great success in routine monitoring programs conducted in French Polynesia: in Nuku Hiva Island, for instance, SPATT devices filled with HP20 resin and deployed for 24h to six days have allowed confirming the presence of dissolved P-CTXs, 44-methylgambierone (formerly known as MTX3, see section 2.1.2), okadaic acid (OA) and dinophysistoxin-1 (DTX1) in the ciguateric spot of Anaho Bay (Roué et al., 2018c, Roué et al, submitted).

Fig. 6

In summary, the complementary use of these two types of passive field-samplers has proved its efficiency in various French Polynesian study sites, including in remote, difficult to access and widely dispersed islands. Combined with analytical tools such as LC-MS/MS (available through a number of specialized laboratories in the region) they can allow early detection of a wide range of toxigenic organisms and related phycotoxins likely to emerge in a given location before their significant bioaccumulation in the food web. Therefore, extending this approach to other Pacific countries where CP is highly prevalent appears as a relevant strategy, since establishing random fish testing surveys on a regular basis in these endemic areas to prevent CP outbreaks seems unrealistic, and beyond the capacity of most of these island states. This management option also offers the possibility to involve local residents in the survey effort, *e.g.*, in the framework of citizen science programs, to ensure sustainable results.

5.1.3 Laboratory detection tools

A common management practice to prevent unsafe products from being placed in the market is to establish a fish ban and/or maximum levels of CTXs in fish flesh (Rodríguez et al., 2017). But unlike other toxins routinely monitored for seafood safety purpose, CTXs are still not regulated due mainly to the lack of a validated reference method and the limited availability of reference CTX standards (Daneshian et al., 2013; Nicolas et al., 2014; Rodríguez et al., 2017; Suzuki et al., 2017). Fortunately, purification efforts aiming at the production of reference material and/or quantified standards from cultures of highly toxic strains of *Gambierdiscus* and/or toxic fish material are currently underway in a few laboratories (Kato and Yasumoto, 2017; Chinain et al., 2018).

Several laboratory detection tests are currently available to assess CTX contents in fish samples, including functional assays (*e.g.*, CBA-N2A, RBA), analytical methods (*e.g.*, LC/MS-MS), and immunoassays based on antibodies recognition (Daneshian et al., 2013; Nicolas et al., 2014; Rodríguez et al., 2017; Tsumuraya and Hirama, 2019). However, implementing sustainable monitoring programs necessarily involves selecting a test best suited to the context of PICTs, *i.e.*, endemic ciguatera zones with often limited resources and technological capacities. In this respect, high throughput screening methods, or bioassays that can be easily transported, stored and used by island communities thus appear as the best candidates.

(a) RBA, F-RBA, CBA

Toxin assessment in seafood classically used the *in vivo* MBA, but due to ethical issues and questionable extrapolation of quantitative risk to humans, the use of an analytical method, *i.e.*, LC-MS/MS, was recommended by the European Food Safety Authority (EFSA) in 2015 (Daneshian et al., 2013; Nicolas et al., 2014). Although LC-MS/MS is a very sensitive method and is helpful for confirming the identity of toxins, it does not allow the detection of currently unknown marine biotoxins. Thereby, alternative methods with high throughput capacity combined with high sensitivity, *e.g.*, CBA-N2a and rRBA, were developed (Daneshian et al., 2013; Nicolas et al., 2014).

The CBA-N2a which uses a murine neuroblastoma (N2a) cell line offers multiple advantages: besides being a good alternative to the MBA when assessing the overall toxicity of a sample, it is also remarkably flexible in detecting a wide range of marine toxins: since its first introduction in the 1990s, this functional assay has been successfully applied to the detection of toxins acting on VGSC (*e.g.*, saxitoxins, tetrodotoxin, CTXs, brevetoxins) (Jellett et al., 1992), palytoxin (Ledreux et al., 2009; Pawlowiez et al., 2013), MTXs (Caillaud et al., 2010), okadaic acid, azaspiracids, pectenotoxins, yessotoxines and dinophysistoxins (Sérandour et al., 2012; Bodero et al., 2018a; Bodero et al., 2018b). The CBA-N2a is also suitable for the detection of CTXs or CTX-like compounds in a variety of biological matrices including *Gambierdiscus* (Caillaud et al., 2009; Rhodes et al., 2010; Pawlowiez et al., 2013; Xu et al., 2014; Roué et al., 2016; Catania et al., 2017; Dai et al., 2017; Litaker et al., 2017; Pisapia et al., 2017a; Clausing et al., 2018; Reverté et al., 2018), cyanobacteria (Kerbrat et al., 2010; Laurent et al., 2012), fish (Bienfang et al., 2008; Bienfang et al., 2011; Chan et al., 2011; Abraham et al., 2012; Bienfang et al., 2012; Caillaud et al., 2012; Jiang et al., 2012; O'Toole et al., 2012; Mak et al., 2013; Robertson et al., 2014; Bravo et al., 2015; Hossen et al., 2015; Soliño et al., 2015; Hardison et al., 2016; Hardison et al., 2018; Loeffler et al., 2018; Díaz-Asencio et al., 2019a; Estevez et al., 2019; Loeffler et al., 2019; Sanchez-Henao et al., 2019; Sanchez-Henao et al., 2020), giant clams (Laurent et al., 2012; Roué et al., 2016; Roué et al., 2018b), gastropods (Darius et al., 2018b), sea urchins (Pawlowiez et al., 2013; Darius et al., 2018a), lobsters and crabs (Mak et al., 2013), sharks (Diogène et al., 2017), and even samples derived from passive sampling devices (Caillaud et al., 2011; Roué et al., 2018c). Another key advantage of the CBA-N2a concerns the possibility to use a cost effective approach when the testing of a high number of samples is required: first, the sample extracts are tested for the presence or absence of CTXs (qualitative random screening) which allows to classify them into negative, suspect or positive samples. Second, a quantitative analysis can then be carried out only on suspect and positive samples, thus saving time and effort.

The rRBA is based on the competitive binding between CTXs and radiolabeled brevetoxin on site 5 of VGSCs, thus allowing the specific detection of any toxin able to interfere with this labeled brevetoxin (Dechraoui et al., 1999; Darius et al., 2007; Nicolas et al., 2014; Dechraoui Bottein and Clausing, 2017; Díaz-Asencio et al., 2018). So far, the rRBA has been successfully applied to the detection of CTXs or CTX-like compounds in *Gambierdiscus* (Darius et al., 2007; Chinain et al., 2010a; Chinain et al., 2010b; Pawlowiez et al., 2013; Díaz-Asencio et al., 2019a; Díaz-Asencio et al., 2019b), cyanobacteria (Laurent et al., 2008; Laurent et al., 2012), fish (Darius et al., 2007; Laurent et al., 2012; Darius et al., 2013; Gaboriau et al., 2014; Clausing et al., 2016; Clausing et al., 2018; Díaz-Asencio et al., 2019a) and giant clams (Laurent et al., 2012). Of note, the rRBA was recently developed into a high throughput testing format (microplates) by Díaz-Asencio et al. (Díaz-Asencio et al., 2018; Díaz-Asencio et al., 2019a; Díaz-Asencio et al., 2019b). However, license requirements and restrictive regulations pertaining to radioisotope utilization represent major issues that can significantly limit the applicability of the rRBA in certain laboratories, especially in PICTs where radioactive waste management could be unaffordable. A fluorescence-based RBA (fRBA) was recently developed as an alternative method for the screening of CTXs in fish samples (McCall et al., 2012; McCall et al., 2014), then successfully applied to the detection of CTXs in Caribbean fish (Hardison et al., 2016; Hardison et al., 2018). The fRBA shows clear advantages as compared to the rRBA, such as easier manipulation, shorter testing time and a high throughput testing capacity.

In summary, both CBA-N2a and rRBA have been widely used in risk assessment and management programs conducted in French Polynesian lagoons (Darius et al., 2007; Chinain et al., 2010b; Laurent et al., 2012; Pawlowiez et al., 2013). Of note, toxicity data yielded at these occasions were consistent with the epidemiological data and the local knowledge of local populations with regard to risky fish species and areas. These observations clearly highlight the benefit of incorporating these two functional assays into routine ciguatera risk monitoring programs for increased food safety in PICTs.

(b) Newly developed cell-based functional tests

Recent research efforts have focused on the development of biosensors based on either mammalian cells or yeast cells, whose potentialities are impressive (Gupta et al., 2019).

Lewis et al. (2016) recently developed a new functional bioassay based on the monitoring of changes in the intracellular Ca^{2+} ions levels of SH-SY5Y cells (human neuroblastoma cells) in response to exposure to potentially contaminated samples. This bioassay was successfully applied to the detection of MTXs and CTX-like compounds, even at low levels. These authors also proposed a simplified extraction procedure to isolate toxins present in *Gambierdiscus* samples making the whole process easier and faster.

Cardiomyocytes represent another interesting cell type: the high number of ion channels present in their membranes renders them highly sensitive to toxins acting on ion channels, while their stable beating signal can be used to quantitatively analyze toxicity. Based on this idea, Wang et al. (2015b) developed a novel functional method for the detection of saxitoxin and tetrodotoxin using a cardiomyocyte-based impedance biosensor able to monitor cardiomyocyte growth and beating status in real time. This biosensor was further developed into a robust portable system in 96 wells microplates with high consistency and long-term lifespan (Wang et al., 2015a), which appears promising for the field of marine toxin detection in general due to its high sensitivity, possible high-throughput screening applications and its potential applicability to the detection of CTXs provided specific adaptations are achieved.

In addition to mammalian cell-based assays, microbial biosensors have also been developed and are currently used for the monitoring of marine environment (Balootaki and Hassanshahian, 2014, for review and references therein). These "whole cells" biosensors classically use different types of microorganisms - bacteria or fungi - which can be genetically modified in various ways in order to increase their sensitivity or to incorporate different reporter and transducer capacity (Han et al., 2018). However, eukaryotic cellular models present several relevant advantages. Among them yeasts are especially interesting since they are very resistant to drastic environmental conditions, and very well-known at both genetic and technological levels (Walmsley and Keenan, 2000). Yeasts also share most cellular features and molecular mechanisms with mammalian cells including signaling pathways relevant to sensing various environmental stimuli. Hence, several bioassays and biosensors based on yeast cells are presently in use in various domains of applications including food safety and HABs monitoring. As an example, Richter and Fidler (2015) have reported the development of recombinant *Saccharomyces cerevisiae* strains able to detect structurally complex marine biotoxins such as okadaic acid, pectenotoxin-11 and portimine. These recombinant yeast strains can be set-up in robust and inexpensive high-throughput screens for microalgal biotoxins and novel marine bioactive chemicals (Richter and Fidler, 2015). Recently, taking advantage of the existence in the model yeast *S. cerevisiae* of a close homolog of the targets of CTXs - mammalian VGSCs - new recombinant yeast strains able to detect CTXs produced by *Gambierdiscus* and *Fukuoya* spp. have also been developed (Martin-Yken et al., 2018). These strains need now to be optimized and coupled to a detection system as simple as possible. Provided their suitability as biosensors is confirmed, they offer promising prospects for the development of a low cost field-test in the near future.

(c) Tests based on the effects of ciguatoxins on fish

The detection of CTXs in fish samples not only requires time-consuming extraction and purification steps, but also quantitative analyses carried out on high-tech equipments and by trained and skilled personnel. Hence, alternative strategies aiming at, *e.g.,* the development of biomarkers that reflect the effects of fish exposure to high concentrations of CTXs have been explored by researchers. Results of proteomic and transcriptomic studies conducted on either CP-prone (*Naso brevirostris, Cephalopholis argus, Gymnothorax javanicus*) or amphidromous (*Oryzias latipes*) fish species revealed a strong signal of differential gene expression between toxic and non-toxic individuals, with genes involved, *e.g.,* in detoxification, and immune defense processes (Jiang et al., 2012; Yan et al., 2017; Nuel et al., 2018). Of note, a similar approach has also been applied to mouse primary cortical neurons as a model for mammalian neuronal cells (Rubiolo et al., 2018) and to the blood of CP patients with the idea of developing a potential diagnostic tool (Ryan et al., 2015).

Although promising, these innovative approaches have not yet allowed the characterization of biomarkers specific to CTX exposure.

5.2 Outreach and communication strategies for an effective management of ciguatera: example from French Polynesia

Since 2007, numerous field campaigns have been conducted in various French Polynesian lagoons in the framework of risk assessment and management programs (Chinain et al., 2010b; Pawlowiez et al., 2013; Darius et al., 2018b). They are useful to investigate the etiology of novel poisoning syndromes especially those involving atypical symptoms, or to provide local populations with risk maps of their lagoon, *i.e.*, assist them in identifying (i) infected reef vs. low risk fishing sites; and (ii) fish species or marine invertebrates deemed not edible. The integrated approach routinely used in these field campaigns combines environmental investigations (see section 5.1.2) and toxicological analyses which target a variety of marine products most representative of the food web, and the population's food preferences and local fishing habits (see section 5.1.3a). If exceptional measures are required, fishing bans and/or ciguatera alerts can be issued in close coordination with local authorities (Fig. 7A). In addition to these field investigations, community outreach interventions are also conducted in the form of public meetings (Fig. 7B). At these occasions, recommendations to systematically report CP incidents to the local medical staff are strongly emphasized to the population.

Fig. 7

Other outreach and communication strategies are also currently considered for a more effective prevention of CP risk in French Polynesia. Based on our long-time experience with local communities, providing regular information and warnings about ciguatera all year round appears critical for increased awareness and sustainable results. This is achieved through the dissemination of guide books, flyers and posters made available in French and native language that are displayed at various strategic spots of each island, such as town halls, medical centers, schools, etc. (Fig. 8A).

In parallel, information and education actions targeted at the healthcare workers occupational group are also carried out: in 2018, an online survey was conducted among 88 healthcare professionals in duty in the five islands that compose French Polynesia, in order to identify potential gaps and weaknesses in the existing reporting network. It provided useful information on their level of knowledge about ciguatera (source, symptoms, diagnosis, patient' scare including the potential use of traditional remedy, etc.), and commitment to the reporting program. As a result, a medical information kit along with flyers intended for patients were produced and made available in paper and numeric formats (https://www.service-public.pf/dsp) (Fig. 8B).

Finally, educational interventions are also conducted on a regular basis in the frame of citizen science initiatives, school interventions, "week of science" workshops, etc.

Fig. 8

6 Conclusion

Very few countries in the Pacific region currently have a defined action plan in response to the health threat represented by ciguatera. Among the major obstacles to the implementation of sustainable monitoring and mitigation programs is the lack of sufficient resources due to competing priorities, and technical training on HAB sciences. However, the recent globalization of ciguatera has led to a resurgence of interest within the scientific community and regulatory agencies. As a result, voices have raised for more international coordinated research efforts in the field of ciguatera, as attested by the emergence of regional programs such as the Pace-Net Plus project funded by the European Commission to reinforce EU-Pacific cooperation on Science, Technology, and Innovation (http://plus.pacenet.eu.s3-website-eu-west-1.amazonaws.com/), the SafeFish National Ciguatera Poisoning Research Strategy (http://safefish.com.au/reports/technical-reports/ciguatera-research-strategy), as well as recent international initiatives such as the International Atomic Energy Agency (IAEA) technical cooperation projects, and the Intergovernmental Oceanographic Commission (IOC) of UNESCO, IAEA, FAO, and World Health Organization (WHO) Interagency Global Ciguatera Strategy (http://www.ioc-unesco.org/index.php?option=com_oe&task=viewDocumentRecord&docID=15111/). It is also highly encouraging that at the 32th session of the Codex Committee on Fisheries and Fishery Products (Food and Agricultural Organization of the United Nations (FAO) and World Health Organization (WHO), 2016), CP was raised by the Pacific Nations as an issue that increasingly affects the tropical and subtropical regions of the Pacific Ocean, Indian Ocean, and Caribbean Sea, resulting in a joint data call on ciguatera by both FAO and WHO (http://www.fao.org/fileadmin/user_upload/agns/pdf/Call_for_data_experts/CALL_FOR_DATA_CFP_final-1.pdf). All these initiatives should eventually benefit PICTs by fostering and/or accelerating the implementation of risk assessment and management programs in PICTs.

However, several issues specific to PICTs remained to be addressed: for instance, in PICTs composed of widely dispersed islands, there is an urgent need to establish effective tracking systems to quickly trace fish from harvest locations to retail outlets in the eventuality of a major toxic outbreak, in order to minimize the health impact and economic losses. Additionally, since a significant reduction in IRs was observed on numerous occasions following information and community-outreach interventions (Pawlowiez et al., 2013), the implementation of country-wide prevention programs also represent a good management option, especially in communities where a high level of risk-taking behavior is frequently reported. Similarly, regular training in CP diagnosis among health professionals should be promoted to improve patients' care (Pearn, 1998; Friedman et al., 2017) and to compensate for the high turn-over of the medical personnel generally observed in PICTs. Finally, despite the extensive studies conducted in the Pacific over the past decade, high quality time-series data are still lacking for the region, making this area an ideal playground for scientists where appropriate observer (sentinel) sites can be identified for long-term monitoring programs (Tester et al., 2020).

Improved networking at a regional and international level aroused by the renewed interest in ciguatera will hopefully assist in the implementation of a global response to a global issue.

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