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Review

Domoic acid and human exposure risks: A review

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ABSTRACT

Domoic acid is a potent neurotoxin that is naturally produced by several diatom species of the genus *Pseudo-nitzschia*. The toxin acts as a glutamate agonist and is excitotoxic in the vertebrate central nervous system and other glutamate receptor-rich organs. Human exposure to domoic acid occurs via the consumption of contaminated shellfish that have accumulated the toxin while filter feeding on toxigenic phytoplankton during blooms. The first reported human domoic acid poisoning event occurred in Canada in 1987 during which clinical signs of acute toxicity such as gastrointestinal distress, confusion, disorientation, memory loss, coma and death were observed. The illness was named amnesic shellfish poisoning (ASP) and due to effective seafood monitoring programs there have been no documented ASP cases since 1987. However, domoic acid poisoning has a significant effect on marine wildlife and multiple poisoning events have occurred in marine birds and mammals over the last few decades. Currently, domoic acid producing diatom blooms are thought to be increasing in frequency world wide, posing an increasing threat to wildlife and human health. Of particular concern are the potential impacts of long-term low-level exposure in "at risk" human populations. The impacts of repetitive low-level domoic acid exposure are currently unknown. This review provides a basic description of the mechanism of action of domoic acid as well as a synthesis of information pertaining to domoic acid exposure routes, toxin susceptibility, and the importance of effective monitoring programs. The importance of investigating the potential human health impacts of long-term low-level domoic acid exposure in "at risk" human populations is also discussed.

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1. Introduction

Domoic acid (DA) is a naturally produced algal toxin that is responsible for a human illness known as amnesic shellfish poisoning (ASP). This neurotoxic illness was first identified in 1987 when over 143 people became ill and 4 died after consuming DA-contaminated mussels harvested from cultivation beds on the eastern coast of Prince Edward Island, Canada (Bates et al., 1989; Wright et al., 1989; Perl et al., 1990). Although multiple macroalgal and diatom sources of DA have been identified (see Table 1), toxigenic diatoms pose the biggest threat to human health through the accumulation of DA in filter-feeding marine organisms. Clinical signs of ASP in humans consist of gastrointestinal distress, confusion, disorientation, seizures, permanent short-term memory loss, and in the most severe cases death (Perl et al., 1990).

Toxic blooms of DA-producing diatoms are a global issue (Trainer et al., 2008) and appear to be increasing in frequency and toxicity, thereby presenting a continued threat to human health and seafood safety. This threat is increasingly important as the demand for seafood grows and current increases in aquaculture activities continue throughout the world. On the US West Coast many effective research and monitoring programs for the detection of DA in shellfish and coastal waters have been established (e.g. Washington State Department of Health (WDOH), California

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Table 1
Known primary producers of domoic acid.

Genus and species	Family	Reference
Red algae		
Alsidium corallinum	Rhodomelaceae	Impellizzeri et al. (1975)
Amansia glomerata	Rhodomelaceae	Sato et al. (1996)
Chondria armata	Rhodomelaceae	Takemoto and Daigo (1958)
Chondria baileyana	Rhodomelaceae	Laycock et al. (1989)
Digenea simplex	Rhodomelaceae	Sato et al. (1996)
Vidalia obtusiloba	Rhodomelaceae	Sato et al. (1996)
Diatoms		
Amphora coffeaeformis	Catenulaceae	Bates (2000)
Nitzschia navis-varingica	Bacillariaceae	Kotaki et al. (2000, 2005), Lundholm and Moestrup (2000)
Pseudo-nitzschia australis	Bacillariaceae	Garrison et al. (1992)
Pseudo-nitzschia calliantha	Bacillariaceae	Martin et al. (1990), Lundholm et al. (1997, 2003), Besiktepe et al. (2008)
Pseudo-nitzschia cuspidata	Bacillariaceae	Bates (2000), Lundholm et al. (2003), Schnetzer et al. (2007), Trainer et al. (2009)
Pseudo-nitzschia delicatissima	Bacillariaceae	Rhodes et al. (1996)
Pseudo-nitzschia fraudulenta	Bacillariaceae	Rhodes et al. (1998)
Pseudo-nitzschia galaxiae	Bacillariaceae	Lundholm and Moestrup (2002)
Pseudo-nitzschia multiseries	Bacillariaceae	Bates et al. (1989, 1991, 1993); Bates et al. (2004)
Pseudo-nitzschia multistriata	Bacillariaceae	(Orsini et al., 2002)
Pseudo-nitzschia pseudodelicatissima	Bacillariaceae	Rhodes et al. (1998)
Pseudo-nitzschia pungens	Bacillariaceae	Bates et al. (1989, 1991, 1993); Bates et al. (2004), Rhodes (1998)
Pseudo-nitzschia seriata	Bacillariaceae	Lundholm et al. (1994)
Pseudo-nitzschia turgidula	Bacillariaceae	Rhodes et al. (1998)

Note: some taxonomic discrepancies have been reported in the literature therefore only species that were identified by TEM/SEM and verified to produce domoic acid and or its isomers are listed.

Department of Public Health (CDPH), Olympic Region Harmful Algal Bloom Program (ORHAB), SoundToxins Program, and the Rapid Analysis of *Pseudo-nitzschia* and DA Locating Events in near-Real Time (RAPDALERT) research program). Likewise, Canada has been a leader in developing measures to control DA exposure risks to the seafood consuming public and other countries such as Norway, Scotland, France, Ireland, Portugal, Spain, Japan, Australia and New Zealand have also taken action to monitor and assess DA risks in shellfish (Park, 1995; Toyofuku, 2006). Many regulatory agencies world wide have established biotoxin monitoring programs such as the Canadian Food Inspection Agency, European Food Safety Authority, Food Control Authority Norway, United Kingdom Food Standards Agency, Agency for Food Safety France, Food Safety Authority of Ireland, National Institute for Biological Resources (IPIMAR) Portugal, Community Reference Laboratory of Marine Biotoxins Spain, Food Safety Commission of Japan, Australian Shellfish Quality Assurance Program, New Zealand Food Safety Authority (NZFSA), Food Standards Australia and New Zealand, Food and Drug Administration (FDA) USA, and the World Health Organization Food Safety Program. The increased awareness and implementation of these programs have certainly made a difference and there has not been a documented human ASP episode since the Prince Edward Island incident. Of course it is possible that an ASP event may go unidentified particularly in underdeveloped nations and along vast stretches of coastline where monitoring coverage is sporadic or non-existent. However, in countries with active DA monitoring programs no new ASP episodes have been reported.

Although current monitoring programs appear to be effective at preventing acute DA poisoning in humans, there may be impacts due to repetitive long-term low-level exposure that have yet to be identified. For example, a chronic DA toxicosis syndrome has been characterized in sea lions that is distinguishable from acute toxicosis (Goldstein et al., 2008). The identification of a second form of chronic toxicity reveals the potential for additional manifestations of DA-related disease in other mammalian species. Currently sea lions are being used as a sentinel species for predicting potential human health threats associated with deteriorating ocean conditions at the West Coast Center for Oceans and Human Health (WCCOHH) at the Northwest Fisheries Science Center in Seattle, Washington. Additionally, the development of a vertebrate model for characterizing the impacts of repetitive low-level DA exposure (at doses below those that cause clinical signs of toxicity) is currently underway.

To date, several excellent review articles and book chapters have been written that address various aspects of DA toxicology, pathology, bioaccumulation, and production in toxic diatom species (Hallegraeff, 1993; Todd, 1993; Hasle et al., 1996; Martin et al., 1996; Burk et al., 1998; Clark et al., 1999; Garthwaite, 2000; Van Dolah, 2000; Mos, 2001; Van Dolah and Ramsdell, 2001; Landsberg, 2002; Pravda et al., 2002; Brett, 2003; Friedman and Levin, 2005; Bates and Trainer, 2006; Salzman et al., 2006; Ramsdell, 2007; Bejarano et al., 2008; Pulido, 2008; Ramsdell and Zabka, 2008; Trainer et al., 2008; Vale et al., 2008). The specific goals of this review are to: 1) summarize structure and activity relationships of DA, 2) characterize DA exposure routes and toxin susceptibilities across vertebrate species, 3) discuss current HAB toxin monitoring efforts that are aimed at protecting human health, and 4) identify novel DA exposure hazards for humans.

2. Structure, stability and mode of action

Domoic acid is a water soluble, polar, non-protein excitatory amino acid that is structurally related to kainic acid (Wright et al., 1989; Fig. 1). Domoic acid (DA) was first

isolated from the rhodophyte, *Chondria armata*, following investigations on the antihelmintic and insecticidal activity of seaweed extracts (Takemoto and Daigo, 1958; Daigo, 1959a,b). The molecular structure of DA was determined by NMR (Takemoto and Daigo, 1958; Daigo, 1959c) and then later confirmed following total synthesis (Takemoto et al., 1966; Ohfune and Tomita, 1982). Complete details related to the synthesis and semi-synthesis of DA and its isomers is beyond the scope of this review but can be found elsewhere (Ni et al., 2003; Clayden et al., 2005a,b).

An evaluation of the general chemical characteristics of DA is crucial for understanding the receptor interactions and ultimately the toxic effects of DA in vertebrates. Domoic acid consists of a proline ring, three carboxyl groups and an imino group that can exist in up to five charged states depending on the pH of the solution (Falk et al., 1989; Walter et al., 1992). The DA molecule contains two conjugated double bonds in the side chain and the geometry of these moieties is directly related to the interaction at the glutamate receptor and toxicity of the molecule (Hampson et al., 1992). The presence of these stable dienes enables DA to absorb UV light and at neutral pH has an emission maxima of 242 nm which is utilized in the detection of DA by liquid chromatography (Takemoto and Daigo, 1958; Falk et al., 1989; Walter et al., 1992, 1994; Quilliam, 2003).

Domoic acid is relatively stable and does not degrade at room temperature (Johannessen, 2000; Quilliam, 2003). However, considerable decomposition was reported following exposure to high temperatures (>50 °C) as well as extremely acidic (pH ≤ 2) or alkali (pH ≥ 12) conditions (Quilliam, 2003). Within shellfish tissue, however, the situation is a little different. McCarron and Hess (2006) have shown that conventional steaming and autoclaving at 121 °C of mussel tissue only reduced the total concentration of DA (including epi-DA) by approximately 3%. Based on these data it is clear that cooking will not increase the safety of the shellfish product if contaminated with DA.

Photo-degradation via sunlight-mediated reactions is thought to be the primary route for DA elimination in the marine environment (Bouillon et al., 2006). The effectiveness of photo-degradation of DA has been studied in pure toxin and cultures in the laboratory. Bates et al. (2004) showed that 60–70% DA could be lost in samples over a 10–12-day incubation with continuous irradiance with the primary degradation product being 5′epidomoic acid (Quilliam, 2003). Likewise, DA can be converted to isodomoic acid derivatives when exposed to UV light or heat (Wright et al., 1990; Wright and Quilliam, 1995). To date, ten DA isomers have been identified in marine samples including isodomoic acids A to H and 5′ epi-DA (Maeda et al., 1986; Wright et al., 1990; Zaman et al., 1997). Interestingly, the toxicity of isodomoic acid A, B and C have been shown to be significantly lower than DA itself and as such pose a greatly reduced risk to human health compared to the parent toxin (Munday et al., 2008).

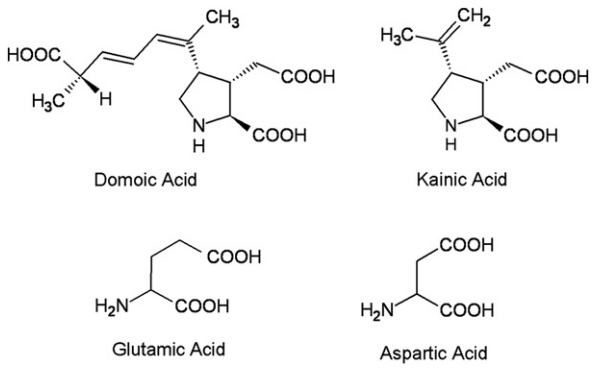

Fig. 1. Structures of domoic acid and related excitatory amino acids.

Due to the structural similarity to kainic acid (KA), glutamic acid (Glu) and aspartic acid (Asp), it is no surprise that DA interacts with the glutamate receptors (Glu_R) on nerve cell terminals (Fig. 1). Glutamate (Glu) is the principal excitatory neurotransmitter in the brain and while a critical component for all synaptic transmission, excessive Glu has been attributed to neurodegeneration (Doble, 1995; Nijjar and Nijjar, 2000; Colman et al., 2005), seizures (Zaczek and Coyle, 1982; Dakshinamurti et al., 1991; Sharma and Dakshinamurti, 1993; Cendes et al., 1995) and apoptosis (Doble, 1995; Nijjar and Nijjar, 2000; Ananth et al., 2001; Colman et al., 2005; Giordano et al., 2007; Giordano et al., 2008). Over-activation of Glu_R's by endogenous Glu or Asp initiates a cascade of biochemical events that can lead to neuronal injury or cell death (Watkins and Evans, 1981; Lipton and Rosenberg, 1994). This is predominantly mediated by excessive influx of Ca^{2+} into neurons through ionic channels that are triggered by activation of Glu_R's. There are two main types of glutamate receptors; 1) ionotropic receptors which are coupled directly to membrane ion channels, and 2) metabotropic receptors coupled to G-proteins that modulate intracellular second messengers and cascades. Domoic acid has been shown to exert excitotoxic effects via activation of ionotropic Glu_R's with the participation and co-activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), kainate and, *N*-methyl-D-aspartate (NMDA) receptor subtypes (Hampson et al., 1992; Tasker et al., 1996; Berman and Murray, 1997; Larm et al., 1997; Hampson and Manalo, 1998; Nijjar and Nijjar, 2000; Berman et al., 2002; Chandrasekaran et al., 2004; Tasker et al., 2005). The rigid structure of DA dramatically reduces the mobility of the molecule when docked at the receptor binding site of glutamate receptors (Carcache et al., 2003) which increases the binding efficacy. The affinity of DA isomers such as isodomoic acid A and C at Kainate and AMPA receptors is much lower than for DA due to the change in stereochemistry that affects the ligand docking within the binding pore (Holland et al., 2005; Sawant et al., 2007). NMDA receptor activated channels permit the influx on Ca^{2+} and Na^{+} into the nerve cell (Choi, 1992, 1994a,b; Zipfel et al., 2000) while AMPA and kainate receptors can be coupled to ion channels that are permeable to Ca^{2+} and so can also contribute to excessive Ca^{2+} entry (Pinheiro and Mulle, 2006; Plested and Mayer, 2007a,b). Despite being only a partial agonist, DA binds to kainate receptors with high affinity and its efficacy is thought to be the result of non-desensitization of the channel (Hampson et al., 1992; Hampson and Manalo, 1998). Domoic acid induced excitotoxicity is reached in a similar manner to Glu and KA, having an integrative action at both sides of the synapse

leading to depolarization and release of Glu into the synapse (Hampson and Manalo, 1998). A rapid influx of Ca^{2+} as a result of DA excitation mobilizes vesicles containing Glu to the membrane surface and is released into the synaptic cleft by exocytosis (Fig. 2). Excessive Ca^{2+} influx causes disruption of Ca^{2+} dependent cascades responsible for neuronal death including membrane, cytoplasmic and nuclear events that result in neurotoxicity. The high concentration of ionotropic Glu_R's in the hippocampus and other brain regions provides the substrate for the selective cellular and neuronal damage observed with DA toxicity and becomes important when considering the manifestation of ASP in vertebrates and humans.

3. Exposure routes for vertebrates

The greatest risk of DA exposure for humans and marine wildlife comes from the dietary consumption of DA-contaminated filter-feeding marine organisms such as shellfish and finfish. A recent paper has also identified the importance of DA accumulation in benthic organisms that could act as vectors to pelagic food webs (Kvitek et al., 2008). A summary of vertebrate consumers in the marine food web that have been shown to contain DA as a result of natural dietary exposures is provided in Table 2. In terms of

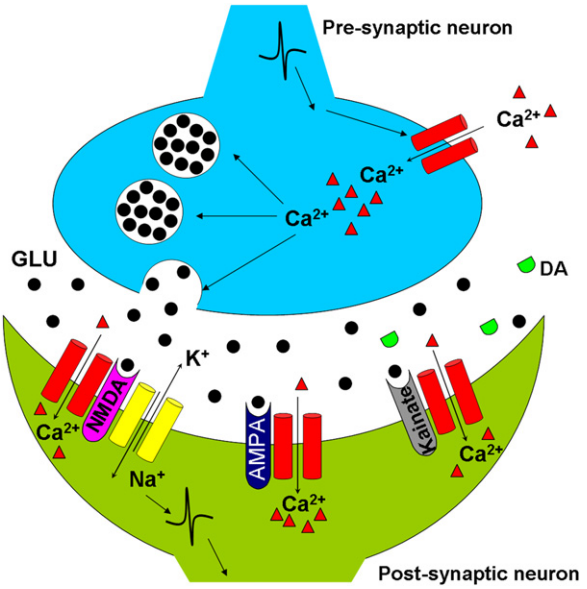

Fig. 2. Basic mechanism of glutamate (GLU) and domoic acid (DA) induced neurotoxicity in nerve cells. Depolarization of the pre-synaptic cell activates the release of endogenous Ca^{2+} which mobilizes vesicles containing GLU to the membrane surface. GLU is then released into the synaptic cleft by exocytosis where it is able to interact with cell surface receptors. Exogenous DA can interact within the synaptic cleft with each of the three ionotropic receptor subtypes including the kainate, AMPA, and NMDA receptors on cell membranes. Activation of the kainate and AMPA receptors results in release of Ca^{2+} via coupled ion channels, into the post-synaptic cell. DA is also able to bind to NMDA receptors that are linked to both Ca^{2+} and NA/K^{+} ion channels and results in a cellular influx of both Na^{+} and Ca^{2+}. Unlike GLU, DA induces prolonged receptor activation causing a constant influx of cations into the cell and the appropriate chemical cues for desensitization are blocked. The excess intracellular Ca^{2+} causes disruption of cellular function, cell swelling and ultimately cell death.

human health risks, vector species such as market squid, scallops, mussels, and razor clams are some of the species of most concern due to their demand by the seafood consuming public (Bargu et al., 2008). Mussels have relatively rapid uptake and depuration rates for DA (Novaczek et al., 1992; Blanco et al., 2002) and so it is fairly straightforward for monitoring programs to protect seafood consumers from DA contamination in this species. Other taxa including anchovies and sand crabs also appear to depurate DA rapidly. In two time course field studies, anchovies and sand crabs were shown to accumulate DA in synchrony with toxic *Pseudonitzschia* blooms with DA levels dropping to undetectable levels within a week of bloom termination (Ferdin et al., 2002; Lefebvre et al., 2002b). Scallops and Razor clams on the other hand have been shown to have slower depurations rates compared to mussels (Wekell et al., 1994; Blanco et al., 2002, 2006; Bogan et al., 2006). In fact, razor clams have been shown to retain DA for up to a year (Wekell et al., 1994). Additionally, DA is found throughout all tissues in the razor clam, whereas a majority of the toxin is confined in the viscera in mussels and fish. The wide variation in tissue distribution and depuration rate of DA in commercially important species necessitates species-specific studies before effective regulatory programs can be employed. For example, geoducks (*Panopea abrupta*) are currently being considered for increased aquaculture purposes in the Pacific Northwest region of Washington State. Clearly an understanding of species-specific toxin tissue distribution and uptake and depuration rates in emerging aquaculture species is imperative in order to effectively manage these fisheries and protect human health.

4. Vertebrate susceptibility

In the aftermath of the Prince Edward Island ASP event, numerous laboratory-based toxicity studies were performed in order to characterize the potency of DA in various vertebrate species. Since 1987, DA exposure studies have been performed in monkeys, mice, rats, birds, and fish (Iverson et al., 1990; Tryphonas et al., 1990a; Tasker et al., 1991; Xi et al., 1997; Lefebvre et al., 2001; Schaffer et al., 2006). Exposure regimes have included; intraperitoneal and direct brain injections, as well as intravenous, intra-arterial, intrauterine, and oral dosing (Sutherland et al., 1990; Dakshinamurti et al., 1993; Suzuki and Hierlihy, 1993; Truelove and Iverson, 1994; Clayton et al., 1999; Lefebvre et al., 2001, 2007). Obviously it is important to understand the effect of these different routes of administration. However, a direct comparison of DA sensitivity between vertebrate species has been difficult to accomplish due to the use of multiple exposure regimes in laboratory-based studies. Several clinical signs of DA neurobehavioral excitotoxicity as a result of DA exposure have been reported, the most notable being vomiting and seizures in humans, scratching and seizures in rodents, vomiting in monkeys, spiral-swimming in fish and tremors in birds (Grimmelt et al., 1990; Perl et al., 1990; Tryphonas et al., 1990a,b; Dakshinamurti et al., 1991; Lefebvre et al., 2001; Silvagni, 2003). Clearly dietary exposure is the most ecologically relevant route of exposure to use when trying to assess

Table 2
Summary of birds, marine mammals, and finfish found to contain domoic acid via natural exposure. For a comprehensive list of shellfish species shown to contain domoic acid see Landsberg (2002) and Table 12-2 in Trainer et al. (2008).

Organism	Region	Reference study
Birds		
Brown pelican (*Pelicanus occidentalis*)	California, USA Cabo San Lucas, Mexico	Work et al. (1993), Sierra-Beltran et al. (1997)
Brandt's cormorant (*Phalacrocorax penicillatus*)	Central California	Work et al. (1993)
Marine mammals		
Blue whale (*Balaenoptera musculus*)	California, USA	Lefebvre et al. (2002a)
Humpback whale (*Megaptera novaengliae*)	California, USA	Lefebvre et al. (2002a)
Dwarf sperm whale (*Kogia sima*)	Southeastern & mid-Atlantic Coast, USA	Fire et al. (2009)
Pygmy sperm whale (*Kogia breviceps*)	Southeastern & mid-Atlantic Coast, USA	Fire et al. (2009)
Bottlenose dolphin (*Delphinus capensis*)	Sonora, Mexico	Sierra-Beltran et al. (2004)
Minke whale (*Balaenoptera acutorostrata*)		Cordaro and Berman (unpublished data from the NMFS National Marine Mammal Health and Stranding Program)
Common dolphin (*Delphinus*)	California, USA	Cordaro and Berman (unpublished data from the NMFS National Marine Mammal Health and Stranding Program)
Harbor porpoise (*Phocoena phocoena*)	California, USA	Gulland (unpublished data)
California sea lion (*Zalophus californianus*)	California, USA	Lefebvre et al. (1999), Scholin et al. (2000)
Northern fur seal (*Callorhinus ursinus*)	California, USA	Gulland and Lefebvre (unpublished data)
Sea otter (*Enhydra lutris*)	California, USA	Lefebvre (unpublished data)
Fish		
Albacore (*Thunnus alalunga*)	California, USA	Lefebvre et al. (2002a)
Anchovy (*Engraulis mordax*)	California, USA	Lefebvre et al. (2002b)
Chub mackerel (*Scomber japonicus*)	California, USA Cabo San Lucas, Mexico	Sierra-Beltran et al. (1997), Lefebvre et al. (2002a), Busse et al. (2006)
Curlfin turbot (*Pleuronectes decurrens*)	California, USA	Vigilant and Silver (2007)
Dover sole (*Microstomus pacificus*)	California, USA	Vigilant and Silver (2007)
English sole (*Pleuronectes vetulus*)	California, USA	Vigilant and Silver (2007)
European sardine (*Sardina pilchardus*)	Portugal	Vale and Sampayo (2001), Costa and Garrido (2004)
Jack mackerel (*Trachurus symmetricus*)	California, USA	Busse et al. (2006)
Jack smelt (*Atherinopsis californiensis*)	California, USA	Lefebvre et al. (2002a)
Lonespine combfish (*Zaniolepis latipinnis*)	California, USA	Busse et al. (2006)
Pacific halibut (*Hippoglossus stenolepis*)	California, USA	Vigilant and Silver (2007)
Pacific sanddab (*Citharichthys sordidus*)	California, USA	Lefebvre et al. (2002a), Busse et al. (2006), Vigilant and Silver (2007)
Pacific sardine (*Sardinops sagax*)	California, USA	Lefebvre et al. (2002b)
Petrale sole (*Eopsetta jordani*)	California, USA	Vigilant and Silver (2007)
Rex sole (*Errex zachirus*)	California, USA	Vigilant and Silver (2007)
Sand sole (*Psettichthys melanostictus*)	California, USA	Vigilant and Silver (2007)
Staghorn sculpin (*Leptocottus armatus*)	California, USA	Fire and Silver (2005)
Slender sole (*Eopsetta exillis*)	California, USA	Vigilant and Silver (2007)
White croaker (*Genyonemus lineatus*)	California, USA	Fire and Silver (2005)

potential human health risks, but there appear to be vast differences in DA tolerances with dietary exposure between vertebrate species (Table 3). These differences are important to consider when developing oral dose animal models for establishing human health protection standards.

Based on the available data from oral dose toxicity studies, humans appear to be more sensitive to DA and experience excitotoxic effects at doses several times lower than rodent mammalian model species and fish (Table 3). When used as an agent to kill intestinal parasites, DA doses of approximately 0.4–0.8 mg/kg body weight were given to Japanese children with no apparent adverse effects (Daigo, 1959a). During the Prince Edward Island ASP event, dietary doses of 0.2–0.3 mg/kg also appeared to have no observable effects, while 0.9–2.0 mg/kg doses resulted in mild GI problems and 1.9–4.2 mg/kg doses caused confusion, disorientation, and seizures (Table 3). In contrast, mice and rats can tolerate oral doses of 28–60 mg/kg without observable adverse effects (Iverson et al., 1989). There are no available estimates for oral dose exposures that are known to induce clinical signs of toxicity in marine mammals. However, the fact that DA poisoning has been a recurrent problem for California sea lion populations in Central California suggests that they are at least as sensitive to DA as humans and may be a good sentinel species for assessing DA-induced human health impacts (Gulland et al., 2002).

In addition to neurobehavioral impacts, DA toxicity has also been shown to induce histopathological effects in the vertebrate central nervous system (CNS) (Pulido, 2008). Most of the studies performed to characterize histopathology associated with DA excitotoxicity have utilized systemic exposures in traditional mammalian model species (Tryphonas et al., 1990a,b; Strain and Tasker, 1991; Friedberg and Ross, 1993; Scallet et al., 1993; Schmued et al., 1995; Wang et al., 2000; Cheng et al., 2002; Qiu and Curras-Collazo, 2006). However, natural dietary exposures associated with toxigenic *Pseadonitzschia* blooms have also confirmed the presence of DA-induced lesions in the CNS of

Table 3
Clinical signs of toxicity associated with oral domoic acid (DA) exposure in multiple vertebrate species.

Organism	Oral dose (mg DA/kg body wt)	Clinical signs of toxicity	Reference study
Humans	0.2–0.3	No observable effect	Perl et al. (1990), Teitelbaum (1990), Todd (1993)
	0.9–2.0	Mild GI symptoms	
	1.9–4.2	Seizure, disorientation	
Monkeys	0.75	No observable effect	Truelove et al. (1997)
	1.0	Vomiting	
Mice	28	No observable effect	Iverson et al. (1989)
	35	Scratching/seizures	
Rats	60	No observable effect	Iverson et al. (1989)
	80	Seizures	
Salmon	10–12	No observable effect	Lefebvre et al. (2007)

humans and marine mammals (Teitelbaum et al., 1990; Scholin et al., 2000; Silvagni et al., 2005; Goldstein et al., 2008). Despite differences in exposure routes and species examined, there appears to be general agreement in terms of histopathological lesion development in neuronal tissue of vertebrates. Other target sites for DA toxicity include the retina (Tryphonas et al., 1990b,c; Polischuk et al., 1998; Silvagni et al., 2005) and cardiovascular system (Perl et al., 1990; Teitelbaum, 1990; Teitelbaum et al., 1990; Nijjar et al., 1999; Kreuder et al., 2005). For an excellent detailed review of DA-induced CNS histopathology and anatomical distributions of lesions see Pulido (2008).

5. Protecting human health

To protect seafood consumers following the Canadian ASP event of 1987, authorities established an action limit for DA of 20 μg DA/g shellfish tissue. Levels exceeding this limit were then intended to trigger closure of the affected beaches and shellfish harvesting areas. Retrospective estimation of DA concentrations in mussels which had caused illness during the ASP outbreak (200 μg DA/g mussel) provided the basis for the action limit and incorporates an approximately 10-fold safety factor (Wekell et al., 2004). The regulatory limit of 20 μg DA/g shellfish tissue has since been adopted by others and is currently enforced in the United States, European Union, New Zealand and Australia for DA in a variety of shellfish species including mussels, scallops, oysters and a variety of clams. However, the original estimates of the human tolerable daily intake (TDI) of DA in seafood revealed that shellfish such as razor clams (*Siliqua patula*) and dungeness crabs (*Cancer magister*) were different. For example, the suggested TDI level for clams was 19.4 μg DA/g tissue, whereas for crab viscera (including hepatopancreas), the suggested TDI level was 31.5 μg DA/g tissue (Marien, 1996). These differences can be attributed to the variation in the uptake, storage and elimination processes between the two organisms and also account for the likelihood that when clams are harvested, large portions (up to 270 g) are eaten in one meal, compared to crabs where one individual would more commonly be consumed (Marien, 1996). In the US Pacific Northwest, the accepted tolerable clam and crab DA levels of 20 μg DA/g tissue and 30 μg DA/g tissue, respectively, have been adopted by the US FDA and WDOH to protect the public from primary health effects associated with DA toxicity. Reducing the human risk of ASP however requires routine shellfish monitoring to provide an early warning of DA contamination and, while a key part of the process, retrospective tissue analyses alone cannot achieve this. Conversely, phytoplankton monitoring can provide an adequate early warning of a bloom, but alone does not provide sufficient protection to the public health risk of ASP. For this reason, phytoplankton surveys are combined with intensive sampling of indicator species such as mussels using a variety of analytical methods to determine the accumulated levels of DA in a particular part of the coast. Undoubtedly, the rapid, reliable detection of DA and estimation of the cumulative toxicity of DA isomers as well as validation of these methods for use on a global scale is of great importance.

Traditionally, the mouse bioassay was used for determination of toxicity in shellfish destined for human consumption. However in the case of DA, this method is highly insensitive and does not provide a reliable estimate of potency or dose response. Many alternative analytical and in vitro assay methods have been developed to ensure that accurate quantitative measurements can be made for the ASP toxin class. At present a reversed phase liquid chromatography method with ultraviolet or diode array detector has become the accepted regulatory method of choice (Quilliam et al., 1989; Wright and Quilliam, 1995; Quilliam, 2003). These methods can be costly due to the need for advanced instrumentation and laboratory infrastructure, expertise required in addition to organic solvents, analytical columns and consumables necessary for analysis. Analysis time itself can also be time consuming when considering transport of samples from more remote areas, sample preparation and clean-up. All of these factors impact the time from sampling to analysis and can therefore delay action and reporting to public and commercial entities alike. Until we reach a clear understanding of bloom dynamics and occurrences in coastal zones, monitoring programs will require both regular and continuous sampling regimens which while crucial to preventing human exposure, increase the financial burden to the respective region. Some monitoring programs such as the Olympic Region Harmful Algal Blooms Partnership (ORHAB) that exists in Washington State, USA, are aimed at developing and implementing the use of rapid detection

methods such as competitive enzyme linked immunosorbent assays (cELISA), portable biosensors and lateral flow rapid tests (e.g. Jellett ASP test strips) that can screen extracts on site. Positive extracts from these tests can initiate beach or clam bed closures immediately while samples are sent to an approved laboratory for confirmatory analysis. This two-tiered approach can minimize the time delays between sample collection and regulatory action and thereby reduce the likelihood of market recalls or human exposure. Clearly there is a global need for the implementation of detection methods that allow real time, on site analyses so that action can be taken by industry and regulatory agencies alike. Moreover, laboratory and field based studies aimed at the understanding of DA production, up-regulation and elimination require timely analysis of numerous and diverse sample matrices. Table 4 provides a comparison of some of the most frequently reported methods for the routine analysis of DA. Clearly, the combined efforts of phytoplankton identification and enumeration, toxin monitoring and quantitative sampling are crucial to managing DA contamination. Likewise, a detailed understanding of bloom dynamics and oceanic processes is required to ensure that the location of sampling is both relevant to shellfish harvesting sites and bloom dynamics, and frequent enough to provide sufficient notification to the public and closures when necessary.

6. Low-level exposure hazards

In terms of human health risks, coastal Tribal communities, such as those in the Pacific Northwest region of Washington State, are likely the most "at risk" human populations for potential toxic impacts of DA exposure. For many Pacific Northwest Native American communities, shellfish are a major source of protein in the diet. In fact, the Quinault phrase ta'a Wshi xa'iits'os means "clam hungry," and illustrates the strong cultural reliance on razor clams for food. Currently, clam dig openings are guided by the toxin regulatory limit of 20 μg DA/g shellfish tissue that is enforced by the Washington State Department of Health (WDOH). When DA levels are $<$20 μg/g, ceremonial and subsistence harvests for razor clams are opened and allow for Tribal members to collect a limit of 100 razor clams per person per dig. These clams are then prepared fresh for ceremonial meals as well as frozen or canned and potentially eaten on a daily basis throughout the year (J. Schumacker, Quinault Tribe, pers. comm.). The question is, what are the impacts of consuming shellfish containing low levels of DA (e.g. 19 μg/g and lower) over a lifetime? Particular concern lies in infants and children that may be exposed. A previous study has shown that DA crosses the placenta, enters the brain tissue of prenates, and accumulates in the amniotic fluid of mammals (Maucher and Ramsdell, 2007). Additionally, it has been documented that DA is transferred to milk after oral exposure in the mammalian rat model (Maucher and Ramsdell, 2005). Currently, a multi-year epidemiological study designed to test whether or not low-level DA exposure via razor clam consumption has human health impacts in a Pacific Northwest Tribal population is underway (Grattan et al., 2007). Preliminary surveys have revealed that the population under study is at risk for low-level DA exposure. Additionally, this study will address whether or not infants born in years when DA levels in coastal razor clams were above the regulatory limit had lower mental development indices than infants born in other years (Grattan et al., 2003). These types of epidemiological studies are ongoing and will hopefully provide conclusive results in terms of health impacts caused by long-term low-level DA exposure. Conversely, it cannot be discounted that potentially healthful benefits of a diet rich in seafood may counter these effects or enhance other physiological parameters (Oken et al., 2008). Additionally, there is evidence that low doses of DA can induce a pharmacological pre-conditioning effect in the brain (Kerr et al., 2002; Sawant et al., 2007), thus increasing the tolerance and reducing the excitotoxic action of higher doses.

An additional study led by the Pacific Northwest Center for Human Health and Ocean Studies at the University of Washington (PNWH2O-UW) in collaboration with the WDOH is underway to assess DA exposure risks to human populations via fish consumption surveys. The study was designed to characterize fish consumption patterns among Asian sub-populations (i.e., Japanese and Korean women of childbearing age in the Puget South area in Washington state). Study participants provided detailed fish consumption data as well as biomarkers of fish intake by giving hair and urine samples used for fatty acid analyses. The preliminary results indicate that mean fish consumption rates for the Japanese and Korean sub-populations assessed (73 and 82 g/day, respectively) are above the national average (Tsuchiya et al., 2008). PNWH20-UW will be evaluating which species are consumed by these sub-populations, and in what amounts, to estimate potential for DA exposure and risk (Elaine Faustman, pers. comm.).

In addition to epidemiological studies, toxicity studies with the zebrafish (*Danio rerio*) vertebrate model are currently underway at the WCCOHH-NWFSC to characterize the impacts of long-term repetitive exposure to low levels of DA. This new model utilizes gene expression as a biomarker for DA-induced toxic insult in the vertebrate CNS. Acute DA exposure (at doses causing neurobehavioral signs of toxicity) has been shown to affect gene expression in previous studies in mice (Ryan et al., 2005). However, studies examining DA exposure impacts on gene expression at doses below those known to induce clinical signs of toxicity (asymptomatic doses) are needed to determine if low-level exposure is a concern. A pilot study supported by the WCCOHH-NWFSC and the PNWH2O-UW examined a single point symptomatic and asymptomatic DA exposure in zebrafish and revealed DA-induced gene expression differences in brain tissues of both treatments compared to control brain (Lefebvre et al., 2009). Not only were both treatments impacted, but low dose asymptomatic zebrafish had expression patterns that were different from high dose treated fish, suggesting a unique mode of toxicity for low-level exposure. The data generated in this study suggested that several biochemical pathways could be impacted at DA doses below those that cause observable signs of behavioral injury. Several genes involved in important subcellular processes, such as immune function, RNA processing, ion transport, metabolism, and signal transduction, where

Table 4
Comparison of some of the most commonly reported methods for the analysis of domoic acid. SH = shellfish extracts, PP = phytoplankton extracts, DP = dissolved phytoplankton, OT = other tissue extracts, BL = blood, U = urine, F = feces, B = bile, FS = food supplements.

Method	LOD (ng DA/mL)	Working range (μg DA/mL)	Matrix	Advantages	Disadvantages
Mouse bioassay[a]	NA	>0.2	SH, PP	Provides an estimate of total toxicity.	Insensitive, non-specific, non-confirmatory, high variability between mice, ethical concern, low throughput.
Direct cELISA[b]	~0.01	0.00001–0.01	SH, PP, DP, OT, BL, U, B, F	High sensitivity, relatively high throughput, selective for DA with little interference, robust, suitable for a variety of matrices.	Non-confirmatory method, small working range so assay re-runs are often required when high DA levels are present.
Jellett ASP test strips[c]	~200	0.2–15	SH	Portable field test, minimal expertise required for use and data collection. Correlates well with LC–UV data.	Qualitative data. Expensive (~$27 USD/sample) for a single non-confirmatory test.
Liquid chromatography–UV_{DAD}[d]	~10	0.01–10	SH, PP, DP, OT, BL, U, B, F	Accurate, high resolution, accepted regulatory method, highly reproducible.	Need specialized and expensive equipment, high maintenance costs, matrix effects, sample clean-up required.
Radio-ligand binding assay[e]	~5	0.005–0.2	SH, PP, DP, OT, BL, U, B, F	Rapid throughput, highly reproducible, high sensitivity, measurement is stable, no time dependent urgency for measurement.	Use of a tritiated ligand requires a regulated laboratory with personnel trained in radiation safety, scintillant waste and radioactive waste disposal can be problematic. Confirmatory method required.
LCMS/MS[f]	~2	0.002–10	SH, PP, OT, BL, U, B, F	Provides structural confirmation (MS/MS), high sensitivity, high resolution, quantitative for all isomers. Can be analyzed simultaneously with other toxin groups.	Ionization suppression by matrix requires clean-up, highly skilled operators, low sample throughput. Need well-established infrastructure, specialized and expensive equipment, high maintenance costs.
Capillary electrophoresis–UV_{DAD}[g]	~150	0.15–8	SH, FS	No clean-up required, sample dilution is sufficient and matrix is eliminated during the run, high resolving power (10× lower than LC–UV) reduced buffer/solvent use.	Requires coupling to MS for confirmation.

[a] Leftly and Hannah (1998).
[b] Garthwaite et al. (1998, 2001), Kleivdal et al. (2007a,b).
[c] Rafuse et al. (2004).
[d] Quilliam et al. (1989), Wright et al. (1989), Wright and Quilliam (1995), Quilliam (2003).
[e] Van Dolah et al. (1997), Baugh et al. (2004).
[f] Thibault et al. (1989); Pleasance et al. (1990); Hess et al. (2001); Holland et al. (2003); Ciminiello et al. (2005).
[g] Nguyen et al. (1990); Zhao et al. (1997); Pineiro et al. (1999); Gago-Martinez et al. (2003).

significantly downregulated as a result of low-level DA exposure, thus indicating potential neurological risk associated with asymptomatic exposures (Lefebvre et al., 2009). One specific gene, the zebrafish homolog of human NDRG4, was markedly downregulated in the zebrafish model and has been associated with memory-related disease (Lefebvre et al., 2009). Further studies are being performed to characterize whole brain gene expression patterns associated with long-term repetitive low-level DA exposure in an effort to identify biomarkers of chronic exposure and for assessing potential human health risks to DA-induced disease.

7. Summary

The increased public awareness of the healthful benefits of seafood has generated a significant and growing demand for seafood products globally. Concurrently, DA-producing algal blooms are increasing in frequency and expanding in geographic extent. Vertebrate susceptibility to DA along with these factors highlight the need for effective monitoring of seafood, as well as an understanding of human exposure hazards. In addition to the classic description of acute DA toxicity, this review identifies the importance of examining the impacts of long-term low-level DA exposure for which there is little information. Current research efforts using advanced technologies such as microarray analysis for the development of gene biomarkers of low-level exposure together with epidemiological studies with "at risk" human populations will allow for a more complete assessment of DA impacts on human health.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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