Chapter 26: Natural Toxins

Updated:

Potential Food Safety Hazard

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Marine biotoxins

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Contamination of fish with natural toxins from the harvest area can cause consumer illness. Most of these toxins are produced by species of naturally occurring marine algae (phytoplankton). They accumulate in fish when they feed on the algae or on other fish that have fed on the algae. There are also a few natural toxins which are naturally occurring in certain species of fish.

There are five recognized fish poisoning syndromes in the United States: paralytic shellfish poisoning (PSP), neurotoxic shellfish poisoning (NSP), diarrhetic shellfish poisoning (DSP), amnesic shellfish poisoning (ASP), and ciguatera fish poisoning (CFP). Scombrotoxin formation, the subject of Chapter 27, is not considered a natural toxin (FDA, 2001).

Amnesic shellfish poisoning (ASP)

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Amnesic shellfish poisoning is generally associated with the consumption of molluscan shellfish from the northeast and northwest coasts of North America. It has not yet been a problem in the Gulf of Mexico, although the algae that produces the toxin has been found there. ASP toxin has

recently been identified as a problem in the viscera of Dungeness crab, tanner crab, red rock crab, and anchovies along the west coast of the United States. The viscera of anchovies are also eaten (FDA, 2001).

Domoic acid produced by dense growth of an algae in the genus *Pseudonitzschia* causes ASP. In the early stages of ASP, the individual usually experiences intestinal distress. Severe ASP can cause a facial grimace or chewing motion, short-term memory loss and difficulty breathing. Death can occur (Ward et al., 1997).

Diarrhetic shellfish poisoning (DSP) Top

Diarrhetic shellfish poisoning is generally associated with the consumption of molluscan shellfish. There has been no documented occurrence to date in the U.S. However, instances have been documented in Japan, southeast Asia, Scandinavia, western Europe, Chile, New Zealand, and eastern Canada (FDA, 2001).

A number of algae species in the genera *Dinophysis* and *Prorocentrum* have been associated with DSP. These algae are responsible for the production of a number of toxins, including okadaic acid and its derivatives. The symptoms of DSP are diarrhea, nausea, vomiting, moderate to severe abdominal pain and cramps, and chills. No known fatalities have occurred, and total recovery is expected within three days, with or without medical assistance (Ward et al., 1997).

Neurotoxic shellfish poisoning (NSP) Top

Neurotoxic shellfish poisoning in the U.S. is generally associated with the consumption of molluscan shellfish harvested along the coast of the Gulf of Mexico, and, sporadically, along the southern Atlantic coast. There has been a significant occurrence of toxins similar to NSP in New Zealand, and some suggestions of occurrence elsewhere (FDA, 2001).

NSP is caused by *Gymnodinium breve*. Blooms of this algae usually result in fish kills and can make shellfish toxic to humans. The blooms generally begin offshore and move inshore. *G. breve* produces three known toxins (brevetoxins). NSP resembles a mild case of ciguatera or PSP. Symptoms begin within three hours of consuming contaminated shellfish. Symptoms include: tingling of the face that spreads to other parts of the body, cold-to-hot sensation reversal, dilation of the pupils, and a feeling of inebriation. Less commonly, victims may experience: prolonged diarrhea, nausea, poor coordination, and burning pain in the rectum (Ward et al., 1997).

Paralytic shellfish poisoning (PSP) Top

Paralytic shellfish poisoning in the U.S. is generally associated with the consumption of molluscan shellfish from the northeast and northwest coastal regions of the U.S. PSP in other parts of the world has been associated with molluscan shellfish from environments ranging from tropical to temperate waters. In addition, in the U.S., PSP toxin has recently been reported from the viscera of mackerel, lobster, Dungeness crabs, tanner crabs, and red rock crabs. While the viscera of mackerel are not normally eaten, the viscera of lobster and crabs are. However, the levels of PSP toxin that are found in lobster tomale are not likely to pose a health hazard unless large quantities are eaten from a heavily contaminated area (FDA, 2001).

PSP is caused by many species of toxic algae. These include *Alexandrium*, *Pyrodinium* and *Gymnodinium*. PSP can be caused by a combination of any of 18 toxins (saxitioxins), depending on the species of algae, geographic area and type of shellfish involved. Symptoms of PSP initially involve numbness and a burning or tingling sensation of the lips and tongue that spreads to the face and fingertips. This leads to a general lack of muscle coordination in the arms, legs, and neck. A variety of other less commonly reported symptoms also exist. Severe cases of PSP have resulted in respiratory paralysis and death (Ward et al., 1997).

Ciguatera fish poisoning (CFP)

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Ciguatera toxin is carried to humans by contaminated fin fish from the extreme southeastern U.S., Hawaii, and subtropical and tropical areas worldwide. In the south Florida, Bahamian, and Caribbean regions, barracuda, amberjack, horse-eye jack, black jack, other large species of jack, king mackerel, large groupers, and snappers are particularly likely to contain ciguatoxin. These species are not generally associated with ciguatera in the northern Gulf of Mexico. Many other species of large fish-eating fishes may be suspect. In Hawaii and throughout the central Pacific, barracuda, amberjack, and snapper are frequently ciguatoxic, and many other species both large and small are suspect. Mackerel and barracuda are frequently ciguatoxic from mid to northeastern Australian waters (FDA, 2001).

CFP is caused by certain species of tropical and subtropical fish that consume toxic algae or other fish that have become toxic. The algae species most often associated with CFP is *Gambierdiscus toxicus*, but others are occasionally involved. There are at least four known toxins that concentrate in the viscera, head, or central nervous system of affected fish. Ciguatera causes: diarrhea, abdominal pain, nausea, vomiting, abnormal or impaired skin sensations, vertigo, lack of muscle coordination, cold-to-hot sensation reversal, muscular pain, and itching. Some of the symptoms may recur for as long as six months. Death is infrequent, but may occur (Ward et al., 1997).

Other marine toxins

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There are naturally occurring toxins in some species that do not involve marine algae.

Gempylotoxin

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Escolar or oilfish (i.e. *Lepidocybium flavobrunneum*, *Ruvettus pretiosus*) contains a strong purgative oil, called gempylotoxin, that may cause diarrhea when consumed (FDA, 2001).

Tetrodotoxin

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Puffer fish, or fugu, may contain tetrodotoxin. Poisonings from tetrodotoxin have usually been associated with the consumption of puffer fish from waters of the Indo-Pacific ocean regions. However, several reported cases of poisonings, including fatalities, involved puffer fish from the Atlantic Ocean, Gulf of Mexico, and Gulf of California. There have been no confirmed cases of poisonings from *Spheroides maculatus* but there is still reason for concern (FDA, 2001).

Symptoms of poisoning usually begin within 10 minutes of consuming puffer fish. The victim first experiences numbness and tingling of the mouth. This is followed by weakness, paralysis,

decreased blood pressure, and quickened and weakened pulse. Death can occur within 30 minutes (Ward et al., 1997).

Tetramine Top

Tetramine is a toxin that is found in the salivary glands of *Neptunia* spp., a type of whelk. The hazard can be controlled by removing the glands (FDA, 2001).

Control Measures Top

There are no validated, rapid methods that are suitable for shipboard, dockside, or commercial testing of lots of fish for any of these toxins (FDA, 2001).

ASP, DSP, NSP, PSP, and CFP

Natural toxins cannot be reliably eliminated by heat. However, severe heating processes, such as retorting, may be effective at reducing the levels of some natural toxins.

To minimize the risk of molluscan shellfish containing natural toxins from the harvest area, State and foreign government agencies, called Shellfish Control Authorities, classify waters in which molluscan shellfish are found, based, in part, on the presence of natural toxins. As a result of these classifications, molluscan shellfish harvesting is allowed from some waters, not from others, and only at certain times, or under certain conditions, from others. Shellfish Control Authorities then exercise control over the molluscan shellfish harvesters to ensure that harvesting takes place only when and where it has been permitted. Molluscan shellfish include oysters, clams, mussels, and scallops, except where the scallop product contains the shucked adductor muscle only.

Significant elements of Shellfish Control Authorities' efforts to control the harvesting of molluscan shellfish include: 1) a requirement that containers of in-shell molluscan shellfish (shellstock) bear a tag that identifies the type and quantity of shellfish, harvester, harvest location, and date of harvest; 2) a requirement that molluscan shellfish harvesters be licensed; 3) a requirement that processors that shuck molluscan shellfish or ship, reship, or repack the shucked product be certified; and, 4) a requirement that containers of shucked molluscan shellfish bear a label with the processor's name, address, and certification number.

An established water classification system similar to the molluscan shellfish system is not in place for controlling CFP in fin fish. However, some states issue advisories regarding reefs that are known to be toxic. In areas where there is no such advisory system, fishermen and processors must depend on first-hand knowledge about the safety of the reefs from which they obtain fish.

Where PSP or ASP have become a problem in fin fish or crustaceans, states generally have closed or restricted the appropriate fisheries. In addition, removal and destruction of the viscera will eliminate the hazard (FDA, 2001)

Gempylotoxin

FDA advises against importation of escolar (i.e. *Lepidocybium flavobrunneum, Ruvettus pretiosus*) (FDA, 2001).

Tetramine and Tetrodotoxin

FDA makes no recommendations and has no specific expectations with regard to controls for tetrodotoxin or tetramine in processors' HACCP plans (FDA, 2001).

FDA Guidelines

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FDA has established action levels for all of the natural toxins except CFP.

- PSP- 0.8 ppm (80ug/100g) saxitoxin equivalent;
- NSP- 0.8 ppm (20 mouse units/100g) brevetoxin-2 equivalent;
- DSP- 0.2 ppm okadaic acid plus 35-methyl okadaic acid (DXT 1);
- ASP- 20 ppm domoic acid, except in the viscera of Dungeness crab, where 30 ppm is permitted (FDA, 2001).

No fish may be harvested from:

- An area that is closed to fishing by foreign, federal, state, or local authorities; or
- An area that is the subject of a CFP advisory; or
- An area for which you have knowledge that there is a CFP problem.

All shellstock (in-shell molluscan shellfish) must bear a tag that discloses the date and place they were harvested (by State and site), type and quantity of shellfish, and by whom they were harvested (i.e., the identification number assigned to the harvester by the shellfish control authority, where applicable or, if such identification numbers are not assigned, the name of the harvester or the name or registration number of the harvester's vessel). For bulk shipments of shellstock (loose shellstock), the shellstock must be accompanied by a bill of lading or other similar shipping document that contains the same information.

All molluscan shellfish must have been harvested from waters authorized for harvesting by a shellfish control authority. For U.S. Federal waters, no molluscan shellfish may be harvested from waters that are closed to harvesting by an agency of the federal government.

All containers of shucked molluscan shellfish must bear a label that identifies the name, address, and certification number of the packer or repacker of the product.

All molluscan shellfish must be from a harvester that is licensed as required (note that licensing may not be required in all jurisdictions) or from a processor that is certified by a shellfish control authority.

(Note: only the primary processor [the processor that takes possession of the molluscan shellfish from the harvester] need apply controls relative to the identification of the harvester, the harvester's license, or the approval status of the harvest waters.) (FDA, 2001)

FDA issued an industry advisory on puffer fish. (October 2007)NEW

Analytical Procedures

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Amnesic shellfish poisoning

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Bioassay

- Wright et al., 1989

Capillary electrophoresis

- Nguyen et al., 1990
- Quilliam et al., 1992

High performance liquid chromatography

- Domoic acid in mussels: Liquid chromatographic method (AOAC, 1995ci)
- Hartfield et al., 1994
- Lawrence et al., 1989
- Lawrence et al., 1991
- Lawrence et al., 1994
- Lawrence and Ménard, 1991
- Pocklington et al., 1990
- Quilliam et al., 1989a
- Quilliam et al., 1995
- Wright et al., 1989

Immunochemical analysis

- Newsome et al., 1991

Mass spectrometry

- Pleasance et al., 1990a
- Quilliam et al., 1989b
- Thibault et al., 1989
- Wright et al., 1989

Receptor competitive binding assay

- Van Dolah et al., 1994

Thin-layer chromatography

- Dallinga-Hanneman et al., 1993

Diarrhetic shellfish poison

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Cytoxicity assay

- Amzil et al., 1992

Bioassay

- Hamano et al., 1985
- Japanese Ministry of Health and Welfare, 1981
- Kat, 1985
- Vernoux et al., 1993

High performance liquid chromatography

- Allenmark et al., 1990
- Dickey et al., 1993
- Dickey et al., 1994
- Lee et al., 1987
- Luckas, 1992
- Marr et al., 1994
- Quilliam, 1995
- Yasumoto et al., 1989

Immunological assay

- Levine et al., 1988
- Shestowsky et al., 1992
- Shestowsky et al., 1993
- Usagawa et al., 1989

Liquid chromatography - ion-spray mass spectrometry

- Hu et al., 1992
- Marr et al., 1992a
- Marr et al., 1992b
- Pleasance et al., 1990b
- Pleasance et al., 1992b
- Quilliam, 1995

Phosphatase inhibition assay

- Boland et al., 1993
- Holmes, 1991
- Honkanen et al., 1996
- Luu et al., 1993
- Simon and Vernoux, 1994

Thin Layer Chromatography

- Quilliam and Wright, 1995

Neurotoxic shellfish poison

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- Mouse bioassay (Tester and Fowler, 1990; Delaney, 1985).
- Radioimmunoassay (Poli and Hewetson, 1992).
- Sodium channel cell viability assay (Manger et al., 1993; Manger et al., 1995).
- Sodium channel competitive binding assay (Poli et al., 1986).

Paralytic shellfish poison

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- Paralytic shellfish poison: Biological method (AOAC, 1995cj).
- Paralytic shellfish poison: Liquid chromatography/mass spectrometry (Pleasance et al., 1992a).
- Paralytic shellfish poison: Liquid chromatography/mass spectrometry (Thibault et al., 1991).
- Sodium channel cell viability assay (Manger et al., 1993; Manger et al., 1995; Manger et al., 2003).

Ciguatera fish poison

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- Mouse bioassay (Yasumoto et al., 1984).
- Liquid chromatography - mass spectrometry (Musser et al., in preparation).
- Sodium channel cell viability assay (Manger et al., 1993; Manger et al., 1995).
- Sodium channel competitive binding assay (Lewis et al., 1991).
- Immunological assay (Hokama, 1993)

Commercial Test Products

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Commercial test products for Ciguatoxin.

As of March 8, 2011, currently there are no test kits for ciguatoxins that are reliable and thus none successfully validated either. There is an effort in Japan to develop an ELISA kit based on synthesized ciguatoxins and impressive progress, but to date it has not reached adequate sensitivity to detect the ciguatoxins at levels to protect human health. There are powerful research tools, for example cytotoxicity assay that have the required sensitivity and together with LC-MS/MS have been applied in studying outbreaks, but these are not rapid portable tests. New action levels and more guidance are being proposed but have not been released yet. The current guidance from FDA for those who haven't seen it is at:
http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/Seafood/FishandFisheriesProductsHazardsandControlsGuide/default.htm

Research on ciguatera and method development for the ciguatoxins severely impacted by lack of the purified toxins.

Commercial test products for Diarrhetic Shellfish Poison.

Test Kit	Analytical Technique	Approx. Total Test Time	Supplier
DSP Rapid KIt [Quantifiable limit 0.1ug/g digestive gland]	Colorimetric phosphatase inhibition assay	80 min including sample prep	SCETI K.K. DF Kasumigaseki Place, 3-6-7 Kasumigaseki Chiyoda-ku, Tokyo 100-0013 Phone: 81-3-3310-2652 E-mail: jhkim@sceti.co.jp Web: www.sceti.co.jp/medical

Commercial test products for Domoic Acid

Test Kit	Analytical Technique	Approx. Total Test Time	Supplier
Biosense ASP ELISA kit [Used for the quantitative analysis of domoic acid (DA) and epi-DA. Suitable for the analysis of shellfish, algea and saltwater. Can also be used for the analysis of mammalian body fluids.]	Direct competitive ELISA	2 h	Biosense Laboratories AS Contact: Ståle Wiborg HIB-Thormohlensgt. 55 N-5008 Bergen, Norway Phone: +47 5554 3966 E-mail: biosense@biosense.com Web: www.biosense.com
JELLETT RAPID TEST for ASP [For qualitative detection of all domoic acid analogues, the causative agent for Amnesic Shellfish Poison (ASP). It detects as low as 1-2 ppm in phytoplankton and 10 ppm in shellfish and fish. May be used on shellfish, phytoplankton and fish.]	Lateral flow immunoassay	≤1 h total time, including sample prep	Jellett Rapid Testing Ltd. Contact: Lisa Horn, Marketing 4654 Route #3 Chester Basin , Nova Scotia Canada B0J 1K0 E-mail: sales@jellett.ca Web: www.jellett.ca

Commercial test products for Okadaic Acid.

Test	Analytical Technique	Approx. Total Test Time	Supplier
DSP-Check [Used for the quantitative analysis of okadaic acid (OA) and its derivate (DTX1) in scallop.]	ELISA	20 min	R-Biopharm, Inc. Contact: Sean Tinkey 7950 US 27 South Marshall, MI 49068 Phone: 877/789-3033 E-mail: sales@r-biopharm.com Web: www.r-biopharm.com

Commercial test products for Saxitoxin.

Test	Analytical Technique	Approx. Total Test Time	Supplier
JELLETT RAPID TEST for PSP [For qualitative detection of all saxitoxins, the causative agent for paralytic shellfish poison (PSP), as low as 40µg/100grams. May be used on shellfish, phytoplankton and fish.]	Lateral flow immunoassay	≤1 h total time, including sample prep	Jellett Rapid Testing Ltd. Contact: Lisa Horn, Marketing 4654 Route #3 Chester Basin , Nova Scotia Canada B0J 1K0 E-mail: sales@jellett.ca Web: www.jellett.ca
RIDASCREEN® FAST Saxitoxin (PSP) [Sensitive and quantitative determination of Saxitoxin (PSP)]	Immunoassay	1 h	R-Biopharm, Inc. Contact: Sean Tinkey 7950 US 27 South Marshall, MI 49068 Phone: 877/789-3033 E-mail: sales@r-biopharm.com Web: www.r-biopharm.com

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