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SEAFOOD TOXINS

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Our resident expert on this subject, Dr. Robert Price, has retired and since died. He based his presentation on excerpts from the US FDA "Bad Bug Book," and for the time being, I shall do the same.

The URLs of the appropriate sections are:

- Shellfish-associated toxins — http://www.cfsan.fda.gov/~mow/chap37.html
- Scombroid poisoning — http://www.cfsan.fda.gov/~mow/chap38.html
- Ciguatera poisoning — http://www.cfsan.fda.gov/~mow/chap36.html
- Tetrodotoxin (pufferfish) — http://www.cfsan.fda.gov/~mow/chap39.html

These are presented according to my perceptions of their relative risks to US consumers (most to least risk). Links have been deleted, but are available in the on-line originals, at the FDA web site.

Bibliography

Johnson, E. A., and E. J. Schantz. 2002. Seafood toxins. pp. 211–230. *In* Cliver, D. O., and H. P. Riemann, eds. 2002. Foodborne Diseases, 2d ed., Academic Press, London.

Johnson, E. A., and E. J. Schantz. 2006. Miscellaneous natural intoxications. pp. 663–709. *In* Riemann, H. P., and D. O. Cliver, eds. Foodborne Infections and Intoxications, 3d ed. Academic Press (Elsevier), London, Amsterdam.

VARIOUS SHELLFISH-ASSOCIATED TOXINS

1. Name of the "Organism":
Various Shellfish-Associated poisoning is caused by a group of toxins elaborated by planktonic algae (dinoflagellates, in most cases) upon which the shellfish feed. The toxins are accumulated and sometimes metabolized by the shellfish. The 20 toxins responsible for paralytic shellfish poisonings (PSP) are all derivatives of saxitoxin. Diarrheic shellfish poisoning (DSP) is presumably caused by a group of high molecular weight polyethers, including okadaic acid, the dinophysis toxins, the pectenotoxins, and yessotoxin. Neurotoxic shellfish poisoning (NSP) is the result of exposure to a group of polyethers called brevetoxins. Amnesic shellfish poisoning (ASP) is caused by the unusual amino acid, domoic acid, as the contaminant of shellfish.

2. Nature of Acute Disease: Types of Shellfish Poisoning:
Paralytic Shellfish Poisoning (PSP)
Diarrheic Shellfish Poisoning (DSP)
Neurotoxic Shellfish Poisoning (NSP)
Amnesic Shellfish Poisoning (ASP)

3. Nature of Disease:
Ingestion of contaminated shellfish results in a wide variety of symptoms, depending upon the toxins(s) present, their concentrations in the shellfish and the amount of contaminated shellfish consumed. The symptoms associated with DSP, NSP, and ASP are less well characterized than those of PSP.

- PSP, the effects are predominantly neurological and include tingling, burning, numbness, drowsiness, incoherent speech, and respiratory paralysis.
- DSP is primarily observed as a generally mild gastrointestinal disorder, i.e., nausea, vomiting, diarrhea, and abdominal pain accompanied by chills, headache, and fever.
- Both gastrointestinal and neurological symptoms characterize NSP, including tingling and numbness of lips, tongue, and throat, muscular aches, dizziness, reversal of the sensations of hot and cold, diarrhea, and vomiting.
- ASP is characterized by gastrointestinal disorders (vomiting, diarrhea, abdominal pain) and neurological problems (confusion, memory loss, disorientation, seizure, coma).

4. Diagnosis of Human Illness:
Diagnosis of shellfish poisoning is based entirely on observed symptomatology and recent dietary history.

5. Associated Foods: All shellfish (filter-feeding molluscs) are potentially toxic. However,

- PSP is generally associated with mussels, clams, cockles, and scallops
- DSP with mussels, oysters, and scallops
- NSP with shellfish harvested along the Florida coast and the Gulf of Mexico
- ASP with mussels.

6. Relative Frequency of Disease:
Good statistical data on the occurrence and severity of shellfish poisoning are largely unavailable, which undoubtedly reflects the inability to measure the true incidence of the disease. Cases are frequently misdiagnosed and, in general, infrequently reported. Of these toxicoses, the most serious from a public health perspective appears to be PSP. The extreme potency of the PSP toxins has, in the past, resulted in an unusually high mortality rate.

7. Course of Disease and Complications:
- PSP: Symptoms of the disease develop fairly rapidly, within 0.5 to 2 hours after ingestion of the shellfish, depending on the amount of toxin consumed. In severe cases respiratory paralysis is common, and death may occur if respiratory support is not provided. When such support is applied within 12 hours of exposure, recovery usually is complete, with no lasting side effects. In unusual cases, because of the weak hypotensive action of the toxin, death may occur from cardiovascular collapse despite respiratory support.
- DSP: Onset of the disease, depending on the dose of toxin ingested, may be as little as 30 minutes to 2 to 3 hours, with symptoms of the illness lasting as long as 2 to 3 days. Recovery is complete with no after effects; the disease is generally not life threatening.
- NSP: Onset of this disease occurs within a few minutes to a few hours; duration is fairly short, from a few hours to several days. Recovery is complete with few after effects; no fatalities have been reported.
- ASP: The toxicosis is characterized by the onset of gastrointestinal symptoms within 24 hours; neurological symptoms occur within 48 hours. The toxicosis is particularly serious in elderly patients, and includes symptoms reminiscent of Alzheimer's disease. All fatalities to date have involved elderly patients.

8. Target Populations:
All humans are susceptible to shellfish poisoning. Elderly people are apparently predisposed to the severe neurological effects of the ASP toxin. A disproportionate number of PSP cases occur among tourists or others who are not native to the location where the toxic shellfish are harvested. This may be due to disregard for either official quarantines or traditions of safe consumption, both of which tend to protect the local population.

9. Food Analysis:
The mouse bioassay has historically been the most universally applied technique for examining shellfish (especially for PSP); other bioassay procedures have been developed but not generally applied. Unfortunately, the dose-survival times for the DSP toxins in the mouse assay fluctuate considerably and fatty acids interfere with the assay, giving false-positive results; consequently, a suckling mouse assay that has been developed and used for control of DSP measures fluid accumulation after injection of the shellfish extract. In recent years considerable effort has been applied to development of chemical assays to replace these bioassays. As a result a good high performance liquid chromatography (HPLC) procedure has been developed to identify individual PSP toxins (detection limit for saxitoxin = 20 fg/100 g of meats; 0.2 ppm), an excellent HPLC procedure (detection limit for okadaic acid = 400 ng/g; 0.4 ppm), a commercially available immunoassay (detection limit for okadaic acid = 1 fg/100 g of meats; 0.01 ppm) for DSP and a

totally satisfactory HPLC procedure for ASP (detection limit for domoic acid = 750 ng/g; 0.75 ppm).

10. Selected Outbreaks:

- MMWR 40(10):1991 and Errata Notice MMWR 40(14):1991 Paralytic shellfish poisoning (PSP) is a foodborne illness caused by consumption of shellfish or broth from cooked shellfish that contain either concentrated saxitoxin, an alkaloid neurotoxin, or related compounds. This report summarizes outbreaks of PSP that occurred in Massachusetts and Alaska in June 1990.
- PSP is associated with relatively few outbreaks, most likely because of the strong control programs in the United States that prevent human exposure to toxic shellfish. That PSP can be a serious public health problem, however, was demonstrated in Guatemala, where an outbreak of 187 cases with 26 deaths, recorded in 1987, resulted from ingestion of a clam soup. The outbreak led to the establishment of a control program over shellfish harvested in Guatemala.
- The occurrence of DSP in Europe is sporadic, continuous and presumably widespread (anecdotal). DSP poisoning has not been confirmed in U.S. seafood, but the organisms that produce DSP are present in U.S. waters. An outbreak of DSP was recently confirmed in Eastern Canada. Outbreaks of NSP are sporadic and continuous along the Gulf coast of Florida and were recently reported in North Carolina and Texas.
- ASP first came to the attention of public health authorities in 1987 when 156 cases of acute intoxication occurred as a result of ingestion of cultured blue mussels (*Mytilus edulis*) harvested off Prince Edward Island, in eastern Canada; 22 individuals were hospitalized and three elderly patients eventually died.

11. Education and Background Resources:

Loci index for genome *Gonyaulax* spp. Available from the GenBank Taxonomy database, which contains the names of all organisms that are represented in the genetic databases with at least one nucleotide or protein sequence.

12. Molecular Structural Data:

These structures are linked to the on-line original.
Dinophysis Toxin
Brevetoxin
Saxitoxin
Okadaic Acid
Domoic Acid
Yesserotoxin
Pectenotoxin

SCOMBROTOXIN

1. Name of the "Organism": Scombrotoxin

2. Nature of Acute Disease: Scombroid Poisoning (also called Histamine Poisoning)

Scombroid poisoning results from eating foods that contain high levels of histamine and possibly other vasoactive amines and compounds. Histamine and other amines are formed by the growth of certain bacteria and the subsequent action of their decarboxylase enzymes on histidine and other amino acids in food, either during the production of a product such as Swiss cheese or by spoilage of foods such as fishery products, particularly tuna or mahi mahi. However, any food that contains the appropriate amino acids and is subjected to certain bacterial contamination and growth may lead to scombroid poisoning when ingested.

3. Nature of Disease:
Initial symptoms may include a tingling or burning sensation in the mouth, a rash on the upper body and a drop in blood pressure. Frequently, headaches and itching of the skin are encountered. The symptoms may progress to nausea, vomiting, and diarrhea and may require hospitalization, particularly in the case of elderly or impaired patients. [*Mimics allergy*.]

4. Diagnosis of Human Illness:
Diagnosis of the illness is usually based on the patient's symptoms, time of onset, and the effect of treatment with antihistamine medication. The suspected food must be analyzed within a few hours for elevated levels of histamine to confirm a diagnosis.

5. Associated Foods:
Fishery products that have been implicated in scombroid poisoning include the tunas (e.g., skipjack and yellowfin), mahi mahi, bluefish, sardines, mackerel, amberjack, and abalone. Many other products also have caused the toxic effects. The primary cheese involved in intoxications has been Swiss cheese. The toxin forms in a food when certain bacteria are present and time and temperature permit their growth. Distribution of the toxin within an individual fish fillet or between cans in a case lot can be uneven, with some sections of a product causing illnesses and others not. Neither cooking, canning, or freezing reduces the toxic effect. Common sensory examination by the consumer cannot ensure the absence or presence of the toxin. Chemical testing is the only reliable test for evaluation of a product.

6. Relative Frequency of Disease:
Scombroid poisoning remains one of the most common forms of fish poisoning in the United States. Even so, incidents of poisoning often go unreported because of the lack of required reporting, a lack of information by some medical personnel, and confusion with the symptoms of other illnesses. Difficulties with underreporting are a worldwide problem. In the United States from 1968 to 1980, 103 incidents of intoxication involving 827 people were reported. For the same period in Japan, where the quality of fish is a national priority, 42 incidents involving 4,122 people were recorded. Since 1978, two actions by FDA have reduced the frequency of

intoxications caused by specific products. A defect action level for histamine in canned tuna resulted in increased industry quality control. Secondly, blacklisting of mahi mahi reduced the level of fish imported to the United States.

7. Course of Disease and Complications:
The onset of intoxication symptoms is rapid, ranging from immediate to 30 minutes. The duration of the illness is usually 3 hours, but may last several days.

8. Target Populations:
All humans are susceptible to scombroid poisoning; however, the symptoms can be severe for the elderly and for those taking medications such as isoniazid. Because of the worldwide network for harvesting, processing, and distributing fishery products, the impact of the problem is not limited to specific geographical areas of the United States or consumption pattern. These foods are sold for use in homes, schools, hospitals, and restaurants as fresh, frozen, or processed products.

9. Food Analysis:
An official method was developed at FDA to determine histamine, using a simple alcoholic extraction and quantitation by fluorescence spectroscopy. There are other untested procedures in the literature.

10. Selected Outbreaks:

- MMWR 38(9):1989 Scombroid fish poisoning is an acute syndrome resulting from consumption of fish containing high levels of histamine. This report summarizes investigations of two outbreaks of scombroid fish poisoning in Illinois and South Carolina in 1988.
- MMWR 37(29):1988 In July 1987, state and local public health officials in New Mexico investigated two cases of scombroid fish poisoning (histamine poisoning) in persons living in Albuquerque. A husband and wife had become ill within 45 minutes after eating dinner. Their symptoms included nausea, vomiting, diarrhea, headache, fever, flushing, and rapid pulse rate. An investigation by the Albuquerque Environmental Health Department found that the couple had shared a meal of grilled mahi mahi, pasta, salad, water, and wine. Their dog had eaten some of the fish and had vomited. Both of the patients had been treated with Benadryl, activated charcoal, and ipecac in a hospital emergency room. Their symptoms resolved within 36 hours of onset of illness.
- MMWR 35(16):1986 Between December 31, 1985, and January 4, 1986, three restaurants in Alabama and Tennessee received complaints of illness from nine customers and one employee who ate Pacific amberjack fish (also called yellowtail or kahala). One restaurant cook, who did not eat the fish, reported a transient red rash on the hands shortly after handling the fish. Ill persons reported no other menu items in common. The fish meals were prepared by grilling or frying. Three people sought medical evaluation. One had diastolic hypotension, and one had bronchospasm. All three were diagnosed as having food or fish allergy and were treated with an antihistamine. The symptoms of scombroid fish poisoning resemble those of a histamine reaction. Scombroid poisoning is

a response to toxic by-products—not an allergic reaction to fish.

- Several large outbreaks of scombroid poisoning have been reported. In 1970, some 40 children in a school lunch program became ill from imported canned tuna. In 1973, more than 200 consumers across the United States were affected by domestic canned tuna. In 1979–1980 more than 200 individuals became ill after consuming imported frozen mahi mahi. Symptoms varied with each incident. In the 1973 situation, of the interviewed patients, 86% experienced nausea, 55% diarrhea, 44% headaches and 32% rashes.
- Other incidents of intoxication have resulted from the consumption of canned abalone-like products, canned anchovies, and fresh and frozen amberjack, bluefish sole, and scallops. In particular, shipments of unfrozen fish packed in refrigerated containers have posed a significant problem because of inadequate temperature control.

11. Education and Background Resources:

Loci index for genome Available from the GenBank Taxonomy database, which contains the names of all organisms that are represented in the genetic databases with at least one nucleotide or protein sequence.

12. Molecular Structural Data:

This structure is linked to the on-line original.

Scombroid Toxin

CIGUATERA

1. Name of the "Organism": Ciguatera

2. Nature of Acute Disease: Ciguatera Fish Poisoning
Ciguatera is a form of human poisoning that results from eating subtropical and tropical marine finfish which have accumulated naturally occurring toxins through their diet. The toxins are known to originate from several dinoflagellate (algae) species that are common to ciguatera endemic regions in the lower latitudes.

3. Nature of Disease:
Manifestations of ciguatera in humans usually involve a combination of gastrointestinal, neurological, and cardiovascular disorders. Symptoms defined within these general categories vary with the geographic origin of toxic fish.

4. Diagnosis of Human Illness:
Clinical testing procedures are not presently available for the diagnosis of ciguatera in humans. Diagnosis is based entirely on symptomology and recent dietary history. An enzyme immunoassay (EIA) designed to detect toxic fish in field situations is under evaluation by the Association of Official Analytical Chemists (AOAC) and may provide some measure of protection to the public in the future.

5. Associated Foods:
Marine finfish most commonly implicated in ciguatera fish poisoning include the groupers, barracudas, snappers, jacks, mackerel, and triggerfish. Many other species of warm-water fishes harbor ciguatera toxins. The occurrence of toxic fish is sporadic, and not all fish of a given species or from a given locality will be toxic.

6. Relative Frequency of Disease:
The relative frequency of ciguatera fish poisoning in the United States is not known. The disease has only recently become known to the general medical community, and there is a concern that incidence is largely under-reported because of the generally non-fatal nature and short duration of the disease.

7. Course of Disease and Complications:
Initial signs of poisoning occur within 6 hours after consumption of toxic fish and include perioral numbness and tingling (paresthesia), which may spread to the extremities, nausea, vomiting, and diarrhea. Neurological signs include intensified paresthesia, arthralgia, myalgia, headache, temperature sensory reversal and acute sensitivity to temperature extremes, vertigo, and muscular weakness to the point of prostration. Cardiovascular signs include arrhythmia, bradycardia or tachycardia, and reduced blood pressure. Ciguatera poisoning is usually self-limiting, and signs of poisoning often subside within several days from onset. However, in severe cases the neurological symptoms are known to persist from weeks to months. In a few isolated cases neurological symptoms have persisted for several years, and in other cases

recovered patients have experienced recurrence of neurological symptoms months to years after recovery. Such relapses are most often associated with changes in dietary habits or with consumption of alcohol. There is a low incidence of death resulting from respiratory and cardiovascular failure.

8. Target Populations:
All humans are believed to be susceptible to ciguatera toxins. Populations in tropical/subtropical regions are most likely to be affected because of the frequency of exposure to toxic fishes. However, the increasing per capita consumption of fishery products coupled with an increase in interregional transportation of seafood products has expanded the geographic range of human poisonings.

9. Food Analysis:
The ciguatera toxins can be recovered from toxic fish through tedious extraction and purification procedures. The mouse bioassay is a generally accepted method of establishing toxicity of suspect fish. A much simplified EIA method intended to supplant the mouse bioassay for identifying ciguatera toxins is under evaluation.

10. Selected Outbreaks:
- MMWR 47(33):1998 This report summarizes an investigation of this outbreak by the Texas Department of Health (TDH), which indicated that 17 crew members experienced ciguatera fish poisoning resulting from eating a contaminated barracuda.
- MMWR 42(21):1993 Twenty cases of ciguatera fish poisoning from consumption of amberjack were reported to the Florida Department of Health and Rehabilitative Services (HRS) in August and September 1991. This report summarizes the investigation of these cases by the Florida HRS.
- MMWR 35(16):1986 On October 29, 1985, the Epidemiology Division, Vermont Department of Health, learned of two persons with symptoms consistent with ciguatera fish poisoning. Both had eaten barracuda at a local restaurant on October 19.
- MMWR 31(28):1982 On March 6, 1982, the U.S. Coast Guard in Miami, Florida, received a request for medical assistance from an Italian freighter located in waters off Freeport, Bahamas. Numerous crew members were ill with nausea, vomiting, and muscle weakness and required medical evacuation for hospitalization and treatment. The findings were consistent with ciguatera fish poisoning.

TETRODOTOXIN

1. Name of the "Organism": Tetrodotoxin (anhydrotetrodotoxin 4-epitetrodotoxin, tetrodonic acid)

2. Nature of Acute Disease: Pufferfish Poisoning, Tetradon Poisoning, Fugu Poisoning

3. Nature of Disease:
Fish poisoning from eating members of the order Tetraodontiformes is one of the most violent intoxications from marine species. The gonads, liver, intestines, and skin of pufferfish can contain levels of tetrodotoxin sufficient to produce rapid and violent death. The flesh of many pufferfish may not usually be dangerously toxic. Tetrodotoxin has also been isolated from widely differing animal species, including the California newt, parrotfish, frogs of the genus Atelopus, the blue-ringed octopus, starfish, angelfish, and xanthid crabs. The metabolic source of tetrodotoxin is uncertain. No algal source has been identified, and until recently tetrodotoxin was assumed to be a metabolic product of the host. However, recent reports of the production of tetrodotoxin/anhydrotetrodotoxin by several bacterial species, including strains of the family Vibrionaceae, *Pseudomonas* sp., and *Photobacterium phosphoreum*, point toward a bacterial origin of this family of toxins. These are relatively common marine bacteria that are often associated with marine animals. If confirmed, these findings may have some significance in toxicoses that have been more directly related to these bacterial species.

4. Diagnosis of Human Illness:
The diagnosis of pufferfish poisoning is based on the observed symptomology and recent dietary history.

5. Associated Foods:
Poisonings from tetrodotoxin have been almost exclusively associated with the consumption of pufferfish from waters of the Indo-Pacific ocean regions. Several reported cases of poisonings, including fatalities, involved pufferfish from the Atlantic Ocean, Gulf of Mexico, and Gulf of California. There have been no confirmed cases of poisoning from the Atlantic pufferfish, *Spheroides maculatus*. However, in one study, extracts from fish of this species were highly toxic in mice. The trumpet shell *Charonia sauliae* has been implicated in food poisonings, and evidence suggests that it contains a tetrodotoxin derivative. There have been several reported poisonings from mislabelled pufferfish and at least one report of a fatal episode when an individual swallowed a California newt.

6. Relative Frequency of Disease:
From 1974 through 1983 there were 646 reported cases of pufferfish poisoning in Japan, with 179 fatalities. Estimates as high as 200 cases per year with mortality approaching 50% have been reported. Only a few cases have been reported in the United States, and outbreaks in countries outside the Indo-Pacific area are rare.

7. Course of Disease and Complications:

The first symptom of intoxication is a slight numbness of the lips and tongue, appearing between 20 minutes to 3 hours after eating poisonous pufferfish. The next symptom is increasing paraesthesia in the face and extremities, which may be followed by sensations of lightness or floating. Headache, epigastric pain, nausea, diarrhea, and/or vomiting may occur. Occasionally, some reeling or difficulty in walking may occur. The second stage of the intoxication is increasing paralysis. Many victims are unable to move; even sitting may be difficult. There is increasing respiratory distress. Speech is affected, and the victim usually exhibits dyspnea, cyanosis, and hypotension. Paralysis increases and convulsions, mental impairment, and cardiac arrhythmia may occur. The victim, although completely paralyzed, may be conscious and in some cases completely lucid until shortly before death. Death usually occurs within 4 to 6 hours, with a known range of about 20 minutes to 8 hours.

8. Target Populations:
All humans are susceptible to tetrodotoxin poisoning. This toxicosis may be avoided by not consuming pufferfish or other animal species containing tetrodotoxin. Most other animal species known to contain tetrodotoxin are not usually consumed by humans. Poisoning from tetrodotoxin is of major public health concern primarily in Japan, where "fugu" is a traditional delicacy. It is prepared and sold in special restaurants where trained and licensed individuals carefully remove the viscera to reduce the danger of poisoning. Importation of pufferfish into the United States is not generally permitted, although special exceptions may be granted. There is potential for misidentification and/or mislabelling, particularly of prepared, frozen fish products.

9. Food Analysis:
The mouse bioassay developed for paralytic shellfish poisoning (PSP) can be used to monitor tetrodotoxin in pufferfish and is the current method of choice. An HPLC method with post-column reaction with alkali and fluorescence has been developed to determine tetrodotoxin and its associated toxins. The alkali degradation products can be confirmed as their trimethylsilyl derivatives by gas chromatography/mass spectrometry. These chromatographic methods have not yet been validated.

10. Selected Outbreaks:
- MMWR 45(19):1996 On April 29, 1996, three cases of tetrodotoxin poisoning occurred among chefs in California who shared contaminated fugu (pufferfish) brought from Japan by a co-worker as a prepackaged, ready-to-eat product. The quantity eaten by each person was minimal, ranging from approximately 1/4 to 1 1/2 oz. Onset of symptoms began approximately 3–20 minutes after ingestion, and all three persons were transported by ambulance to a local emergency department.
- Pufferfish poisoning is a continuing problem in Japan, affecting 30–100 persons/year. Most of these poisoning episodes occur from home preparation and consumption and not from commercial sources of the pufferfish. Three deaths were reported in Italy in 1977 following the consumption of frozen pufferfish imported from Taiwan and mislabelled as angler fish.