Marine Toxins in Food

Food Toxicology
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Learning Objectives

- Understand the linkage between marine algal toxins and human food poisoning.
- Examine Scombroid fish poisoning
- Examine Ciguatera fish poisoning
- Understand paralytic shellfish poisoning (PSP), neurotoxic shellfish poisoning, diarrhetic shellfish poisoning, encephalopathic or amnesic shellfish poisoning.
- Examine Fugu poisoning (tetrodotoxin).
- Explore other marine toxins.

Introduction

- Some marine animals produce a large number of secondary metabolites
  - Prey capture, defense, pheromones
- Many are avoided
  - Starfish, sea cucumbers…
- Poisonings from ingestion of seafood
  - Epidemics – major public
  - health issues
  - Severe economic impact
  - Severe impact on marine life
  - ~ 14% of all food-borne outbreaks

Major Causes of Seafood-borne Illness

- Live molluscan shellfish
  - *Vibrio* species bacteria
  - Norwalk-like viruses
  - Natural marine toxins***
- Scombroid fish poisoning
- Ciguatera fish poisoning

Estimated US Cases Per Year

Norwalk-like virus	100,000
Scombroid fish poisoning	**8,000**
Ciguatera fish poisoning	**1,600**
Vibrio species	1,060
Hepatitis A	1,000
Salmonella	200
Shigella	200
Clostridium perfringens	200

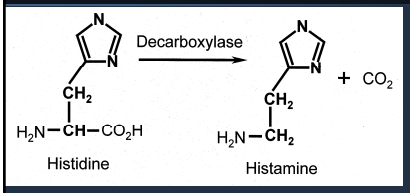
Natural Marine Toxins

- Scombroid fish poisoning (histamine)
- Ciguatera fish poisoning
- Shellfish toxins (ASP, DSP, NSP, PSP)
- Tetrodotoxin
- Gempylotoxin
- *Pfiesteria*

Scombroid Fish Poisoning

- Named for the family Scomberidae (tunas and mackerels)
- Can involve any fish containing high levels of free histidine
- Bacteria break down free histidine into histamine

Histamine Formation



Diamines

Cadaverine

$H_2N–CH_2–CH_2–CH_2–CH_2–CH_2–NH_2$

Putrescine

$H_2N–CH_2–CH_2–CH_2–CH_2–NH_2$

Scombroid Fish Poisoning

- Source: improperly handled (time/temperature abuse) mahi mahi, tuna, bluefish, sardines, mackerel
- Range: worldwide

Scombroid Fish Poisoning

- Onset: immediate to 30 minutes
- Initial symptoms: tingling or burning sensation in the mouth, rash on the upper body, drop in blood pressure, headache, itching of the skin
- Later symptoms: nausea, vomiting, and diarrhea
- Duration: 3 hours to several days

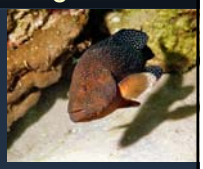
Scombroid Fish Poisoning

- Treatment: antihistamines
- Control: proper chilling and temperature control
- FDA guideline: 50 ppm

Scombroid Poisoning Outbreaks (CDC)

- 5% of all food-borne outbreaks reported and 37% of all seafood-related food-borne illnesses
- Approximately 200 outbreaks of involving nearly 1400 people from 1973-87.
- Between 1988-1997, 145 reported outbreaks involved 811 persons in 20 states.
- Most in HI, FL, CA, WA, NY, CT.

Ciguatera Fish Poisoning



- The most commonly reported marine toxin disease in the world.
  - Associated with consumption of contaminated reef fish.
- 50,000 people per year.
  - Debilitating neurologic symptoms, including profound weakness, temperature sensation changes, pain, and numbness in the extremities.

Ciguatera Fish Poisoning

- Four toxins: complex structures
- Source: certain species of fish feeding on several algae species including *Gambierdiscus*
- Range:
  - Tropical and subtropical waters worldwide
  - U.S.: East coast, Puerto Rico, Hawaii, Virgin Islands
- Toxins: heat stable

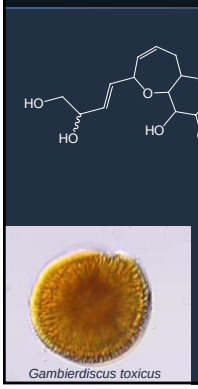
Ciguatoxin

- The dinoflagellate, *Gambierdiscus toxicus* produces ciguatoxin throughout tropical regions of the world.

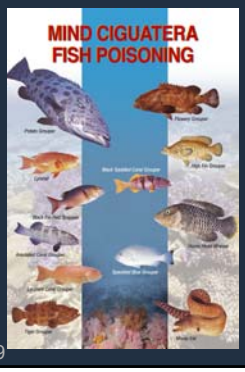
Ciguatoxin

- The two most common toxins associated with Ciguatera are Ciguatoxin and Maitotoxin
  - Some of the most lethal natural substances known (mice 0.45 µg/kg ip).
- Ciguatoxin, a lipid soluble substance, opens voltage dependant sodium channels in cell membranes which induces membrane depolarization.
  - Lethality is usually seen with ingestion of the most toxic parts of fish.
  - Heat stable.

Ciguatoxin


Gambierdiscus toxicus

Ciguatera Fish Poisoning



- Ciguatoxin biomagnifies up the food chain
- Larger, carnivorous fish are primary vectors

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Ciguatera Fish Poisoning

- Onset: <6 hours
- Symptoms:
  - Gastrointestinal: nausea, vomiting, diarrhea
  - Neurological: numbness and tingling around mouth, joint pain, muscle ache, headache, temperature sensory reversal
  - Cardiovascular: arrhythmia, bradycardia, tachycardia, reduced blood pressure

Price

Ciguatera Fish Poisoning

- Duration:
  - Usually self-limiting within several days
  - Rarely some neurological symptoms may persist for months or years
- Treatment:
  - Treat symptoms

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Ciguatera Fish Poisoning

- Control:
  - Mouse bioassay
  - “Cigua-check” test kit available
  - Enzyme immunoassay
  - Obtain fish from safe harvest areas
- Commonly implicated species:
  - Groupers, barracudas, snappers, jacks, mackerel, and triggerfish
- FDA guideline: no guideline

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Ciguatera Outbreaks

- 1981: Puerto Rico, 49 cases, 2 deaths (barracuda, amberjack, blackjack)
- 1987: Caribbean, 57 cases (fish casserole)
- 1988: Florida, >100 cases (hogfish)
- 1992: California, 25 cases (flag cabrilla)
- 1994: California, several cases (yellowtail)
- 1995: Guam (sea weed?)

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Shellfish Toxicity

- Four categories: paralytic, neurologic, diarrheal, and amnestic shellfish poisonings.
- Toxins are found in microscopic diatoms and dinoflagellates with concentrations occurring in filter feeding bivalves, such as clams or mollusks
- Harmful algal blooms (HAB; red tides) are not well-correlated to outbreaks of shellfish poisoning
  - HABs contain toxins

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Harmful Algal Blooms (HAB)

- Most due to dinoflagellates – unicellular microscopic phytoplankton
  - Plant / animal properties
  - Motile
  - Chloroplast
  - High toxin level
- Plankton feeders (shellfish) filter from water → accumulate → up the food chain

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What Triggers the Blooms?

- Multifactorial
  - Nitrogen / phosphorus
  - Metals
  - Vitamins – vitamin B_{12}, thiamin, biotin
  - Temperature
  - pH
  - Quiet, calm conditions
  - Oxygen
  - 'Pristine waters'

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Where Do Red Tides Occur?

- World wide distribution
- Type of dinoflagellate varies with geographical area
- Ocean currents mix with open coast
- Seasonal
  - Warmer conditions
  - May to October – west
  - July to September - east

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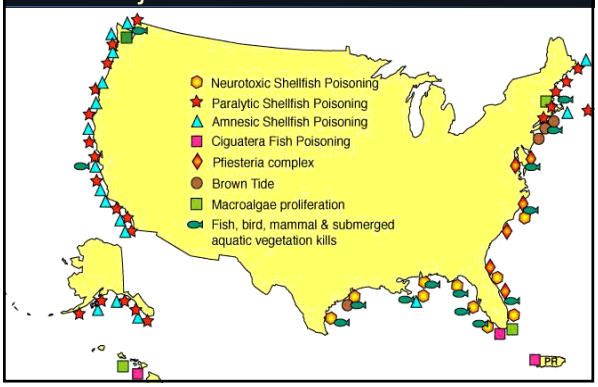
Major US HAB Related Events



Shellfish are the Common Vector

- Filter feeders
  - Clams, oysters, mussels, scallops
- Comprise 7% of all marine intoxications
- Heat stable
- Little effect on the host
- Mortality rates:
  - 8-23%
  - 6% - hospitalization, mechanical ventilation, life support

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Four Major Syndromes

- Paralytic shellfish poisoning (PSP)
- Neurotoxic shellfish poisoning
- Diarrhetic shellfish poisoning
- Encephalopathic or amnesic shellfish poisoning

- Kills fish, birds, mammals

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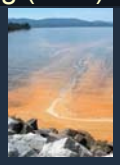
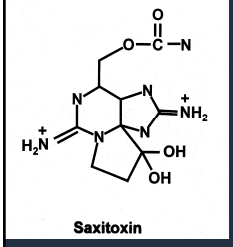
Paralytic Shellfish Poisoning (PSP)

- Most common – severe – fatal
  - ~ 10 per year – CDC
- Dinoflagellates
  - *Alexandrium* – not readily visible
  - *Karenia brevis* – red
- Saxitoxin
  - Sodium channel blockers
  - Heat stable



Paralytic Shellfish Poisoning

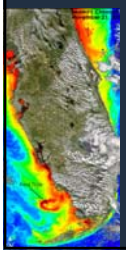


Saxitoxin

- Saxitoxins (12-20 analogs)

Paralytic Shellfish Poisoning

- Source: contaminated molluscan shellfish feeding on algae (*Alexandrium*, *Pyrodinium*, *Gymnodinium* spp.)
- Range: tropical to temperate waters worldwide

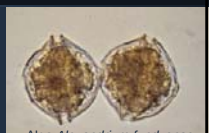


Paralytic Shellfish Poisoning

- Onset: ½ to 2 hours
- Symptoms: tingling, burning, numbness, drowsiness, incoherent speech, respiratory paralysis
- Duration: respiratory support within 12 hours of exposure results in complete recovery; full resolution in a few days to weeks

High Dose PSP

- High dose
  - Difficulty swallowing
  - Difficulty breathing
  - Respiratory paralysis
  - Death – early as 3 to 12 hours
- Case fatality rate: 5%



Alga *Alexandrium fundyense*

Paralytic Shellfish Poisoning

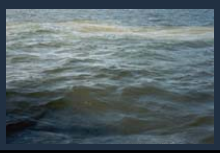
- Control:
  - Mouse bioassay; 10 minute kit; HPLC
  - Monitoring of coastal waters and shellfish
  - Obtain molluscan shellfish from approved waters
- FDA guideline:
  - 0.8 ppm saxitoxin equivalent (80µg/100g) in all fish

PSP Outbreaks

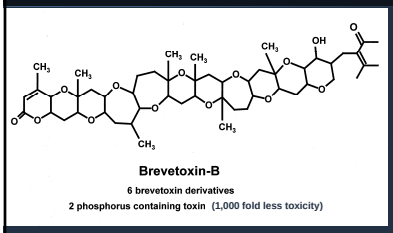
- 1976-89: 42 outbreaks in Alaska
- 1980: California, 98 cases, 2 deaths (oysters)
- 1990: Massachusetts, 6 cases (mussels)
- 1990: Alaska, 11 cases

Neurotoxic Shellfish Poisoning

- Similar to PSP
- Milder
- Dinoflagellate – *Karenia brevis*
- Toxin – brevetoxin
  - Sodium channel blocker
  - Not as potent



Neurotoxic Shellfish Poisoning



Polyether brevetoxins

Neurotoxic Shellfish Poisoning

- Source: molluscan shellfish feeding on algae (*Gymnodinium breve*)
- Range: gulf of Mexico and southern Atlantic coast in U.S.; New Zealand
- Toxins: heat stable

Neurotoxic Shellfish Poisoning

- Onset: a few minutes to a few hours
- Symptoms: tingling and numbness of the lips, tongue, and throat, muscular aches, dizziness, cold hot sensation reversal, diarrhea, vomiting
- Duration: a few hours to several days
- Fatalities: rare

Neurotoxic Shellfish Poisoning

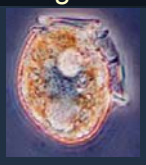
- Control:
  - Mouse bioassay
  - HPLC
  - Commercial immunoassay
  - Obtain molluscan shellfish from approved waters
- FDA guideline:
  - 0.8 ppm brevetoxin-2 equivalent (20 mouse units/100g) in clams, mussels and oysters

Neurotoxic Shellfish Poisoning

- Outbreaks:
  - Sporadic and continuous along the gulf coast of Florida, North Carolina, and Texas

1996 southwest Florida: over 150 Manatee are killed by brevetoxin

Diarrhetic Shellfish Poisoning



- Europe and Japan
- Dinoflagellates
  - *Dinophysis*
  - *Prorocentrum*
- Toxin: okadaic acid derivatives
- Within minutes to hours
  - Diarrhea (92%), Nausea (80%), Vomiting (79%)
- Recovery – 3 days – treat supportively

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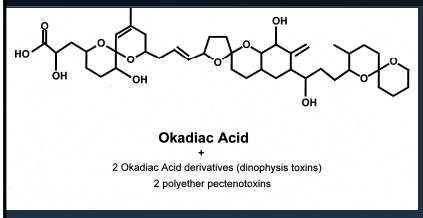
Diarrheic Shellfish Poisoning



Okadiac Acid
+
2 Okadiac Acid derivatives (dinophysis toxins)
2 polyether pectenotoxins

Okadaic acid and its derivatives

45 Price

Diarrheic Shellfish Poisoning

- Source: molluscan shellfish feeding on algae (*Dinophysis* and *Prorocentrum* spp.)
- Range: Japan, southeast Asia, Scandinavia, western Europe, Chile, New Zealand, eastern Canada
- Toxins: heat stable

Price

Diarrheic Shellfish Poisoning

- Onset: 30 minutes to 3 hours
- Symptoms: mild diarrhea, nausea, vomiting, abdominal pain, chills, headache, fever
- Duration: 2-3 days with or without treatment

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Diarrheic Shellfish Poisoning

- Control:
  - Mouse bioassay
  - HPLC procedure
  - Molluscan shellfish from approved waters
- FDA guideline:
  - 0.2 ppm okadaic acid plus 35-methyl okadaic acid (DXT 1) in all fish

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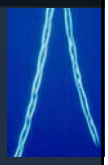
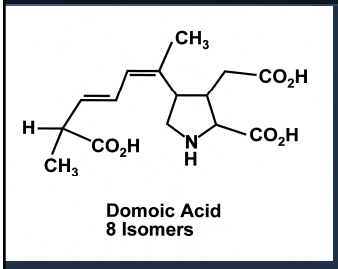
Amnesic shellfish poisoning

- Diatom: *Pseudo-nitzschia* sp.(7) in mussels
- Toxin: domoic acid
- Neurotoxin that acts on excitatory amino acid receptors and on synaptic transmission



Amnesic Shellfish Poisoning



Domoic Acid
8 Isomers

Amnesic Shellfish Poisoning

- Source: Molluscan shellfish (mussels) feeding on algae (*Pseudo-nitzschia* spp.), viscera of Dungeness crab and anchovies
- Range: Northeast and northwest North America

Amnesic Shellfish Poisoning

- Onset:
  - Gastrointestinal symptoms within 24 hours
  - Neurological symptoms within 48 hours
- Symptoms:
  - Gastrointestinal: vomiting, diarrhea, vomiting
  - Neurological: confusion, memory loss, disorientation, seizure coma

Amnesic Shellfish Poisoning

- Duration:
  - Self-limiting within several days
  - Short-term memory loss can be permanent
- Control:
  - HPLC laboratory procedure
  - Obtain shellfish from approved waters
  - Monitoring of coastal water and shellfish

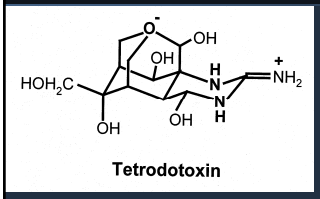
Amnesic Shellfish Poisoning

- FDA guideline:
  - 20 ppm domoic acid in all fish
  - 30 ppm domoic acid in viscera of Dungeness crab
- Outbreaks:
  - 1987: Prince Edward Island, Canada (mussels)
  - 156 cases, 3 deaths, 12 with permanent short-term memory loss
  - 1991: Washington state (razor clams)
  - 24 cases

Fugu (Puffer Fish) Poisoning

- Porcupine fish, ocean sun fish, puffer fish
- Japan
  - Incidence ↓
  - Training cooks – chicken?
  - Sense of exhilaration and euphoria
  - Paraesthesia

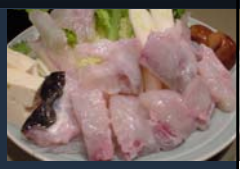
Tetrodotoxin



Tetrodotoxin

Tetrodotoxin

- Tetrodotoxin
  - Highest in liver, gonads
  - Potent sodium channel blocker
- Signs within 15 minutes
  - Paraesthesia
  - Nausea
  - Respiratory paralysis

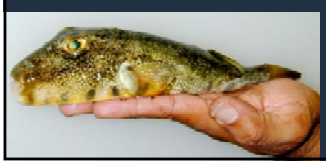


Tetrodotoxin

- Source:
  - Gonads, liver, intestines, and skin of about 80 species of puffer fish, blowfish or fugu
  - Also found in the California newt, parrotfish, frogs (*Atelopus* genus), blue-ringed octopus, starfish, octopus, and xanthid crabs

Tetrodotoxin

- Range:
  - Primarily the Indo-Pacific Ocean
  - Other cases and deaths have occurred from puffer fish from the Atlantic Ocean, Gulf of Mexico, and Gulf of California



Tetrodotoxin

- Onset: 20 minutes to 3 hours
- Initial symptoms: numbness of the lips and tongue
- Secondary symptoms: prickling of the face and extremities, a sensation of lightness or floating, headache, epigastric pain, nausea, diarrhea and/or vomiting
- Tertiary symptoms: increasing paralysis and death within 4-6 hours

Tetrodotoxin

- Control:
  - Mouse bioassay
  - HPLC method
  - Do not eat pufferfish or avoid improperly prepared pufferfish
- FDA guideline:
  - Puffer fish may not be imported except under specific authorization from FDA

Tetrodotoxin Outbreaks

- Japan:
  - 1974-1983, 646 cases, 179 deaths
  - 30-100 persons per year mostly from home preparation and consumption
  - Mortality about 50%
- California:
  - 1996, 3 cases, no deaths

Case Study: Puffer Fish Consumption, 2002

- On March 18, a woman aged 65 years was brought to the hospital by her husband.
- Hours earlier, they had eaten a meal of pufferfish caught in Titusville, FL. Several minutes after eating the fish, both persons experienced tingling around their lips.
- During the next 2 hours, the woman's symptoms worsened, and she developed vomiting.
- The woman developed increasing chest pain and had mild tachycardia and blood pressure of 160/70 mmHg; she was treated with topical nitroglycerine.
- During the next 4--6 hours, she developed an ascending muscular paralysis. A test of her respiratory function indicated carbon dioxide retention and a rapid decrease to <20% of normal vital capacity for a woman her age. She was electively intubated and placed on a ventilator. Over the next day, she regained her reflexes and voluntary movement.
- She was extubated at approximately 72 hours and discharged.

Gempylotoxin

- Toxin: a strong purgative oil contained in the flesh and bones of specific species
- Source: Gemplids, escolars or pelagic mackerels (escolar; oilfish, castor oil fish or purgative fish; snek; 'Ex-Lax fish') 18-21% oil (waxy esters)
- Range: almost worldwide


Escolar

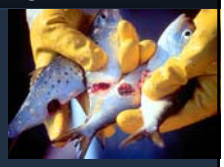
Gempylotoxin

- Symptoms: diarrhea, generally without pain or cramping; ½ to 36 hrs
  - "Keriorrhoea" caused by the wax esters may include oily orange diarrhea, discharge, or leakage from the rectum that may smell of mineral oil.
- Control: avoid specific fish species
- FDA guideline: escolar should not be imported
- Outbreaks: California, 8+ cases, March 2000

Pfiesteria Complex Organisms (PCO)

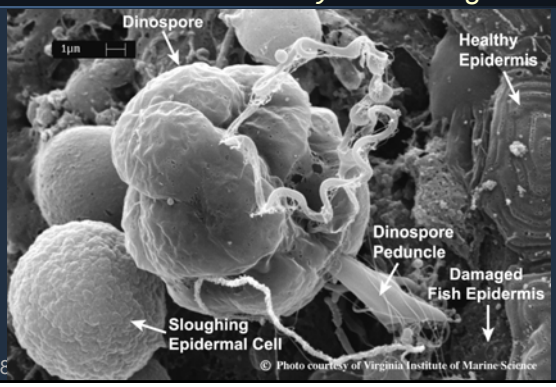
- *Pfiesteria piscicida* discovered in 1988
- Phytoplankton (dinoflagellate)
  - Up to 24 life stages (4 may be toxic)
  - Eats other organisms, usually algae

Pfiesteria Blooms



- *Pfiesteria* may produce toxins that numb fish, allowing the microbes to feed on the fish
  - 2002 micro-predation research
- High concentrations of *Pfiesteria* can cause deep lesions on fish and may kill them
- Blooms usually exist for only a few hours
  - *Several massive fish kills in estuaries along coastal North Carolina*

Pfiesteria shumwayae Feeding



Pfiesteria

- No cases of seafood-borne illness have been reported
- Human health effects have occurred in laboratories where researchers were working in close proximity to high concentrations of the microorganism
- Anglers, water skiers, fish-kill monitors have complained of skin lesions, headaches, lightheadedness, short-term memory loss
- Avoidance recommended