Marine Toxins in Food
Food Toxicology
Instructor: Gregory Möller, Ph.D.
University of Idaho

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

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\begin{align*}
\text{Histamine Formation} \\
\text{Diamines} \\
\text{Cadaverine} & : H_2N-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2 \\
\text{Putrescine} & : H_2N-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2
\end{align*}
\]

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.

**Ciguatera Fish Poisoning**

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

**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

**Ciguatera Fish Poisoning**

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

**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

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?)

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

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

What Triggers the Blooms?
• Multifactorial
  – Nitrogen / phosphorus
  – Metals
  – Vitamins – vitamin B12, thiamin, biotin
  – Temperature
  – pH
Where Do Red Tides Occur?

- Quiet, calm conditions
- Oxygen
- ‘Pristine waters’

• 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

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

Four Major Syndromes

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

- Kills fish, birds, mammals

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

- 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: \(\frac{1}{2}\) 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%

**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
    \((80\mu g/100g)\) 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

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

Diarrheic Shellfish Poisoning

Okadaic acid and its derivatives
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

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

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

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

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**
  – Highest in liver, gonads
  – Potent sodium channel blocker

• **Signs within 15 minutes**
  – Paraesthesia
  – Nausea
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

• 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

• 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

• 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

**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