Domoic Acid (ASP)

- The most recently discovered seafood toxicity (1987)

- 107 cases of acute intoxication after consumption of mussels from Prince Edward Island, CA. 12 severe cases, 5 people died.

- Razor clams and crabs are most often affected by domoic acid

- Domoic acid ingested: 15-20 mg for unaffected persons; 60-110 mg mild symptoms; 135-300 mg serious illness.

- Safety limit: 20 µg/100 g tissue
The Human Episode

AN OUTBREAK OF TOXIC ENCEPHALOPATHY CAUSED BY EATING MUSSELS CONTAMINATED WITH DOMOIC ACID

Trish M. Perl, M.D., Lucie Bédard, M.S.N., Tom Kosatsky, M.D., M.P.H., James C. Hockin, M.D., Ewen C.D. Todd, Ph.D., and Robert S. Remis, M.D., M.P.H.

Abstract  In Canada in late 1987 there was an outbreak of an acute illness characterized by gastrointestinal symptoms and unusual neurologic abnormalities among persons who had eaten cultivated mussels. Health departments in Canada solicited reports of this newly recognized illness. A case was defined as the occurrence of gastrointestinal symptoms within 24 hours or of neurologic symptoms within 48 hours of the ingestion of mussels.

From the more than 250 reports received, 107 patients met the case definition. The most common symptoms were vomiting (in 76 percent of the patients), abdominal cramps (50 percent), diarrhea (42 percent), headache, often described as incapacitating (43 percent), and loss of short-term memory (25 percent). Nineteen patients were hospitalized, of whom 12 required intensive care because of seizures, coma, profuse respiratory secretions, or unstable blood pressure. Male sex and increasing age were associated independently with the risks of hospitalization and memory loss. Three patients died.

Mussels associated with this illness were traced to cultivation beds in three river estuaries on the eastern coast of Prince Edward Island. Domoic acid, which can act as an excitatory neurotransmitter, was identified in mussels left uneaten by the patients and in mussels sampled from these estuaries. The source of the domoic acid appears to have been a form of marine vegetation, Nitzschia pungens, also identified in these waters in late 1987. The contaminated mussels from Prince Edward Island were removed from the market, and no new cases have occurred since December 1987.

We conclude that the cause of this outbreak of a novel and severe intoxication was the ingestion of mussels contaminated by domoic acid, a potent excitatory neurotransmitter. (N Engl J Med 1990; 322:1775-80.)
NEUROLOGIC SEQUELAE OF DOMOIC ACID INTOXICATION DUE TO THE INGESTION OF CONTAMINATED MUSSELS

JEANNE S. TEITELBAUM, M.D., ROBERT J. ZATORRE, PH.D., STIRLING CARPENTER, M.D., DANIEL GENDRON, M.D., ALAN C. EVANS, PH.D., ALBERT GJEDDE, M.D., PH.D., AND NEIL R. CASHMAN, M.D.

Abstract In late 1987 there was an outbreak in Canada of gastrointestinal and neurologic symptoms after the consumption of mussels found to be contaminated with domoic acid, which is structurally related to the excitatory neurotransmitter glutamate. We studied the neurologic manifestations in 14 of the more severely affected patients and assessed the neuropathological findings in 4 others who died within four months of ingesting the mussels.

In the acute phase of mussel-induced intoxication, the patients had headache, seizures, hemiparesis, ophthalmoplegia, and abnormalities of arousal ranging from agitation to coma. On neuropsychological testing several months later, 12 of the patients had severe anterograde-memory deficits, with relative preservation of other cognitive functions. Eleven patients had clinical and electro-myographic evidence of pure motor or sensorimotor neuropathy or axonopathy. Positron-emission tomography of four patients showed decreased glucose metabolism in the medial temporal lobes. Neuropathological studies in the four patients who died after mussel-induced intoxication demonstrated neuronal necrosis and loss, predominantly in the hippocampus and amygdala, in a pattern similar to that observed experimentally in animals after the administration of kainic acid, which is also structurally similar to glutamate and domoic acid.

We conclude that intoxication with domoic acid causes a novel and distinct clinicopathologic syndrome characterized initially by widespread neurologic dysfunction and then by chronic residual memory deficits and motor neuropathy or axonopathy.

• Shellfish Toxins: ASP

Hippocampus Damage

Figure 3. Section of Hippocampus from a Patient Who Died 24 Days after Mussel-Induced Intoxication (Panel A) and from a Normal Subject (Panel B).

In the sample from the patient, there is severe loss of neurons in all fields except $H_2$ (arrow), and tissue collapse is evident in part of field $H_1$ (double arrow). Both sections were stained with Luxol fast blue–cresyl violet ($\times 10$).
Environmental neurotoxins: a role for domoic acid.

Novelli, A., Kispert, J., Reilly, A. and Zitko, V.

Domoic acid-containing toxic mussels produce neurotoxicity in neuronal cultures through a synergism between excitatory amino acids.

Novelli A, Kispert J, Fernández-Sánchez MT, Torreblanca A, Zitko V. 

*Brain Research, 577, 41-48, 1992.*

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ISTITUTO DI SCIENZE, UNIVERSITA' DI TRIESTE, Luglio1989

Neurotossine nei mitili in coltura: il caso dell’acido domoico

Excitatory amino acid toxicity in cerebellar granule cells in primary culture.

Novelli A, Kispert J, Reilly A. and Zitko V.

Domoic Acid (ASP)
- Shellfish Toxins: domoic acid (ASP)
• Shellfish Toxins: domoic acid (ASP)

Ionotropic Glutamate Receptors
Mg²⁺ block of NMDA receptor
Neurotoxicity of Canadian mussels (1987)

Novelli et al. Brain Research 577, 1992
Neurotoxic synergism between Domoic Acid and NMDA receptor agonists
EXCITOTOXICITY BY EAAs: AN HYPOTHESIS

POST SYNAPTIC NON-NMDA RECEPTOR

QUIS

DOMOIC

PRESYNAPTIC NON-NMDA RECEPTOR

POST SYNAPTIC NMDA RECEPTOR

DEPOLARIZATION

Mg^{++}

GLU? ASP? X?

DEPOLARIZATION

RELEASE PROCESS

PERMANENT DEPOLARIZATION

NMDA RECEPTOR

EXOGENOUS NMDA RECEPTOR AGONIST

Na^+ /K^+ PUMP

ATP

CELL DEATH

PRE

Novelli et al. Domoic Acid Toxicity Symposium, Ottawa, 1989
Domoic acid relieves the Mg2+ block at the NMDA receptor
Birds, finfish and marine mammals found to contain domoic acid

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• Shellfish Toxins: domoic acid (ASP)
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Domoic Acid Outbreak Is Killing Thousands of Coastal Animals!!!

Environment (tags: animals, conservation, endangered, pollution, environment, wildlife, water)

Vicky - 1508 days ago - latimes.com

Researchers said today that a virulent outbreak of domoic acid off the California coast is killing thousands of animals and affecting more species of birds than ever before.
Natural Toxins Killing California's Dolphins, Sea Lions
• Shellfish Toxins: domoic acid (ASP)

Is Domoic Acid Dooming Wildlife? – Marina del Rey, CA Patch

News

Is Domoic Acid Dooming Wildlife?

Research aims to identify what causes production of toxin and how to prevent and mitigate it, scientists tell Patch.

By Jacqueline Howard, Nicole Mooradian, and Meredith Skrzypczak | Email the authors | June 1, 2011

Print
The Pacific Marine Mammal Center in Laguna Canyon has received 27 sea lions and eight dolphins with signs of domoic acid poisoning from a harmful algal bloom over the last two weeks. Just two sea lions survived.

“We picked one dolphin up at Bolsa Chica on April 21, and it was having horrible seizures. We had to put that one to sleep. It was dying. We had to do something. They can’t live on land, so for a dolphin having seizures, there is no hope. We put it back in the water and it flipped to its side. It couldn’t even right itself,” said Michelle Hunter, director of the mammal center.
Diarrhetic Shellfish Poisoning Acid (DSP)

- Okadaic acid: $R_1 = H$, $R_2 = H$
- Dinophysistoxin-1: $R_1 = H$, $R_2 = CH_3$
- Dinophysistoxin-3: $R_1 = acyl$, $R_2 = CH_3$

- Pectenotoxin - 1: $R = OH$
- Pectenotoxin - 2: $R = H$

*WHO 84557*
Diarrhetic Shellfish Poisoning (DSP)

- Very lipophilic compounds with a poliether structure
- Produced by dinoflagelates *Dinophysis spp.* or *Prorocentrum*
- Very frequent outbreaks in Europe, causing big economic losses
- Onset: 30 minutes to 3 hours
- Symptoms: mild diarrhea, nausea, vomiting, abdominal pain, chills, headache, fever
- Duration: 2-3 days with or without treatment
- Specific inhibitors of mammalian protein phosphatases 1 and 2A
- FDA guideline: 0.2 ppm okadaic acid plus 35-methyl okadaic acid (DXT 1) in all fish
• Shellfish Toxins: diarrhetic shellfish poisoning (DSP)
Methods of Detection (Monitoring)

- Mouse bioassay still forms the basis of most shellfish toxicity monitoring programmes.
- Official method for PSP and DSP. In Europe, a detailed procedure had been described by the Community Reference Laboratory on Marine Biooxins (CRL-MB) in Vigo, Spain.
  - PSP: 20 g mice are injected i,p an acid extract of the shellfish and the time taken for the animal to die is recorded. Highly toxic extracts are diluted to ensure that mortality occurs within 5 to 15 min. The toxicity of the sample is then calculated with reference to dose response curves.
  - DSP: if at least 2 out of 3 animals die within 24 h after injection, the sample is considered positive for lipophilic algal toxins.
Methods of Detection (Monitoring)

- Limitations of mouse bioassay:
  - Results vary with mouse weight
  - The detection limit of the assay is strain dependent
  - The death time versus toxin level is non-linear
  - It is very labour-intensive to determine accurately the death time
  - The sacrifice of a large number of animals is involved

- Alternative techniques: ELISAs, HPLC, CE-MS, LC-MS, cell cultures... None validated yet for monitoring purposes

- Exception: ASP (domoic acid), official method is by HPLC