Excerpt From:
Diversity of Marine and Freshwater Algal Toxins

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Domoic Acid

Amnesic shellfish poisoning (ASP) is the only shellfish poison produced by a diatom and is currently limited in its distribution to North America (Figure 11). The first recorded occurrence of ASP was in Prince Edward Island, Canada in 1987, when approximately 100 people became ill after consuming contaminated mussels. None of the known shellfish toxins was found to be involved in the outbreak, but rather the toxic agent was identified as domoic acid (95,96). The source of domoic acid was found to be the diatom Pseudo-nitzschia multiseries (formerly known as Nitzschia pungens f. multiseries) (97,98). Domoic acid is a water soluble tricarboxylic amino acid of molecular weight 311, which acts an analog of the neurotransmitter glutamate and is a potent glutamate receptor agonist. Domoic acid was previously identified in the red alga, Chondria armata (99), but had not previously been linked to human illness, and is related both structurally and functionally to the excitatory neurotoxin kainic acid, isolated from the red macroalga Digenea simplex (100). Seven congeners to domoic acid have been identified (Figure 12). Of these, three geometrical isomers, isodomic acids D, E, and F and the C5í diasteriomer are found, in addition to domoic acid, are found in small amounts in both the diatom and inshellfish tissue (101,102).

The symptoms of ASP include gastrointestinal effects (e.g., nausea, vomiting, diarrhea) and neurological effects including dizziness, disorientation, lethargy, seizures, and permanent loss of short term memory. Domoic acid binds with high affinity to both kainate (KD ~ 5 nM) and AMPA (KD ~ 9 nM) subtypes of glutamate receptor (103). Persistent activation of the kainate glutamate receptor results in greatly elevated intracellular Ca2+,through cooperative interactions with NMDA and non-NMDA glutamate receptor subtypes, and voltage dependent calcium channels (104). Neurotoxicity due to domoic acid results in high intracellular calcium and subsequent lesions in areas of the brain where glutaminergic pathways are heavily concentrated, particularly in the CA1 and CA3 regions of the hippocampus (96), an area responsible for learning and memory processing. However, memory deficits occur at doses below those causing structural damage (105). The LD50 (i.p.) for domoic acid in rats is 4 mg/kg; however, the oral potency is substantially lower (35-70 mg/kg) (106). In the 1987 outbreak, human toxicity occurred at 1-5 mg/kg , suggesting that susceptible individuals are more sensitive than rodents to the oral toxicity of domoic acid. Individuals found most susceptible were elderly individuals and those with impared renal function, resulting in poor toxin clearance. Increased susceptibility of elderly individuals appears to be due to impaired toxin clearance as studies in experimental animals and neonates indicate (107).

Since the 1987 outbreak, domoic acid has been identified as the causative agent in the mass mortality of pelicans and cormorants in Monterey Bay, California in 1991 (108,109) and for the extensive die-off of California sea lions in the same region in 1998 (110). The causative organism in both the 1991 and 1998 mortality events was identified as another member of the same diatom genus, Pseudo-nitzschia australis. At least seven species of Pseudo-nitzschia are now recognized as domoic acid producers, and these toxin producing Pseudo-nitzschia species have since been identified in widely diverse geographic areas around the world (reviewed in 111). However, none have been implicated in intoxication events.

As with the other algal toxins discussed in the chapter, the role of domoic acid in the life history of Pseudo-nitzschia is not clear. The production of domoic acid by Pseudo-nitzschia correlates with physiological stress, including silicon or phosphorus limitation, or nitrogen excess. This pattern of synthesis is consistent with classical secondary metabolite biosynthesis by bacteria and other protists, and differs from the constitutive pattern observed in synthesis of polyether toxins by dinoflagellates (2) and PSP toxins (112). In culture, domoic acid is produced primarily in stationary phase, which corresponds with the depletion of Si from the medium (113). The 1987 bloom of Pseudo-nitzschia in Canada was associated with pulses of nitrate from riverine input or resuspended sediments (111). The biosynthesis of domoic acid involves the condensation of acetates via two intermediates, a glutamate derivative from the Krebs cycle and an isoprenoid structure likely derived from geranyl pyrophosphate (114). The precise enzymatic pathways responsible for biosynthesis have not been elucidated.

References:

95. Wright, JLC, RK Boyd, ASW Defrietas, M Falk, RA Foxall, WD Jamieson, MV Laycock, AW McCulloch, AG McInnes, P Odense, V Pathak, MA Quilliam, M Ragan, PG Sim, P Thibault, JA Walter, M Gilgan, DJA Richard, D Dewar. Identification of domoic acid, a neuroexcitatory amino acid, in toxic mussels from eastern P.I.E. Can. J. Chem. 67: 481-490, 1989.

96. Perl, TM, L Bedard, T Kosatsky, JC Hockin, ECD Todd, RS Remic. 1990. An outbreak of toxic encephalopathy caused by eating mussels contaminated with domoic acid. NE J Med 322: 1775-1780.

97. Subba-Rao, DV, MA Quilliam, R Pocklington. 1988. Domoic acid ñ a neurotoxic amino acid produced from the marine daitom Nitzschia pungens in culture. Can J Fish Aquat Sci. 45: 2076-2079.

98. Bates, SS, CJ Bird, ASW Defrietas, R Foxall, M Gilgan, LA Hanic, GR Johnson, AW McCulloch, P Odense, R Pocklington, MA Quilliam, PG Sim, JC Smith, DV Subba Rao, ECD Todd, JA Walter, JLC WrightPennate diatom Nitzschia pungens as the primary source of domoic acid, a toxin in shellfish from eastern Prince Edward Island, Canada. J Fish Aquat Sci 46: 1203-1215, 1989.

99. Takemoto, T., K Daigo. Constituents of Chondria armata and their pharmacologicaleffects. Chem Pharm Bull 6:657-580, 1958.

100. Murakami, S, T Takemoto, Y Shimizu. Studies on the effective principles of Diagenea simplex Aq. I. Separation of the effective fraction by liquid chromatography. J Pharm Soc Japan 73: 1026-1028, 1953.

101. Wright JLC, M Falk, AG McInnes, JA Walter. Identification of isodomoic acid D and two new geometrical isomers of domoic acid in toxic mussels. Can. J. Chem. 68: 22-25, 1990.

102. Walter, JA, M Falk, JLC Wright. Chemistry of the shellfish toxin domoic acid: characterization of related compounds. Can J. Chem. 72:430-436, 1994.

103. Hampson, DR, X Huang, JW Wells, JA Walter, JLC Wright. Interaction of domoic acid and serveral derivatives of kainic acid and AMPA binding sites in rat brain. Eu. J. Pharmacol. 218: 1-8, 1992.

105. Peng YG. J.S.Ramsdell. Brain fos induction is a sensitive biomarker for the lowest observed neuroexcitatory effects of domoic acid. Fund. App. Tox. 31: 162-168, 1996.

106. Xi, D., Y.G. Peng, J.S. Ramsdell. Domoic acid is a potent neurotoxin to neonatal rats. Nat. Toxins 5: 74-79, 1997.

107. Iverson, F, J Truelove, E Nera, L Tryphonas, J Campbell, E Lok. Domoic acid poisoning and mussel-associated intoxication: preliminary investigations into the response of mice and rats to toxic mussel extract. Fd Chem Toxic 27: 377-384, 1989.

108. Fritz L, MA Quilliam, JLC Wright, AM Beale, TM Work 1992. An outbreak of domoic acid and poisoning attributed to the pennate diatom Pseudonitzschia australis. J Phycol 28: 438-442.

109. Work, TM, BB Barr, AM Beale, L Fritz, MA Quilliam, JLC Wright. Epidemiology of domoic acid poisoning in brown pelicans (Pelicanus occidentalis and Brandtís cormorants (Phalacrocorax pencillatus) in California. J Zool Wildlife Med 24: 54-62, 1993..

110. Gulland, F. 1999. Unusual mortality event ñ Domoic acid toxicity in california sea lions (Zalophus californianus) stranded along the central California coast, May-October 1998. Report to U.S. National Marine Fisheries Service Working Group on Unusual Marine Mammal Mortality Events., 30 p.

111. Bates, SS. Bloom dynamics and physiology of domoic acid producing Pseudo-nitzschia species. In: DM Anderson, AD Cembella, GM Hallegraeff, eds. Physiological Ecology of Harmful Algal Blooms. New York: Springer-Verlag, 1998, pp. 267-292.

112. Cembella, AD. 1998. Ecophysiology and mechanism of paralytic shellfish toxins in microalgae. . In: DM Anderson, AD Cembella, GM Hallegraeff, eds. Physiological Ecology of Harmful Algal Blooms. New York: Springer-Verlag, 1998, pp 381-404.

113. Pan, Y, SS Bates, AD CembellaEnvironmental stress and domoic acid production by Pseudo-nitzschia: a physiological perspective. Nat. Toxins 6: 1-9, 1998.

114. Laycock, MV, ASW deFrietas, JLC Wright,. Glutamate agonists from marine algae. J. Appl Phycol 1: 113-122, 1989.

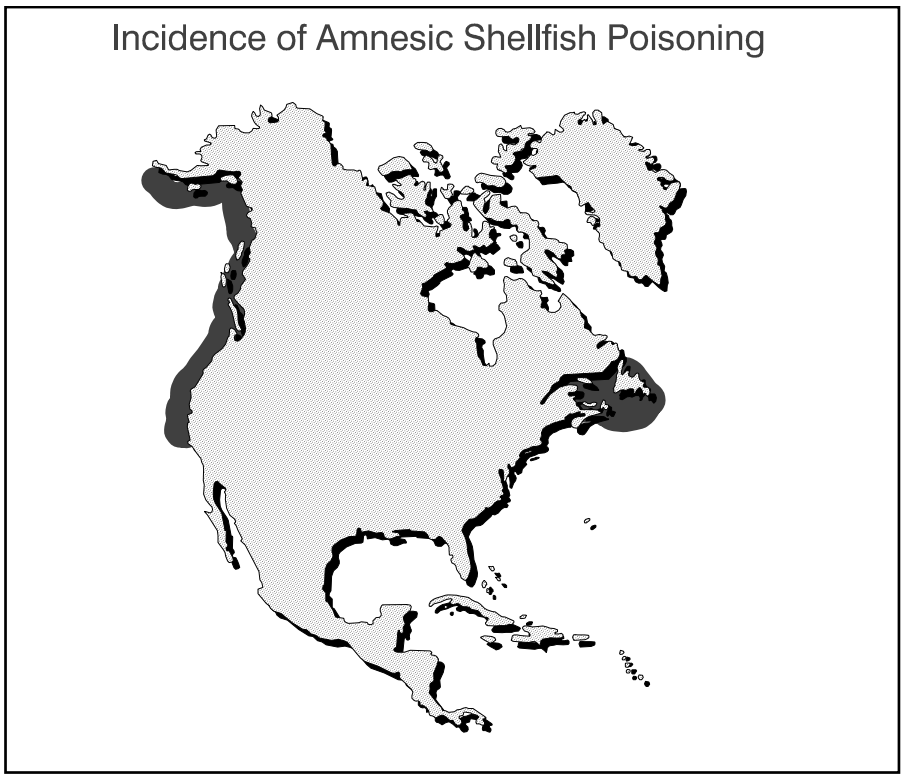

Figure 11. Distribution of ASP.

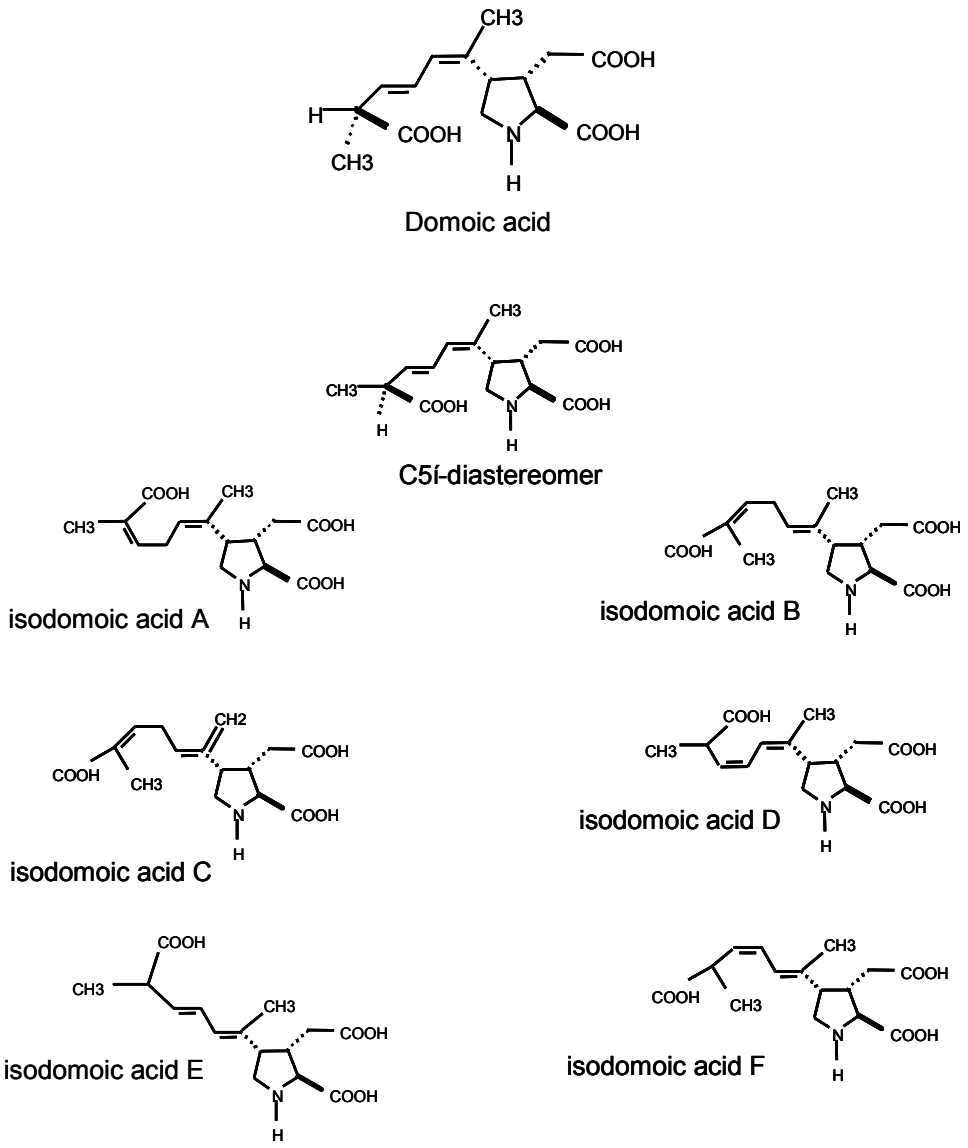

Figure 12. Structures of domoic acid and congeners.