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Invited Perspective: The Relevance of Animal Models of Domoic Acid Neurotoxicity to Human Health

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On 18 August 1961, the *Santa Cruz Sentinel* reported[1] that thousands of "crazed seabirds" were diving into lamp posts, buildings, cars, and streets to their death on the shores of North Monterey Bay, California. The birds appeared to be confused and disoriented, exhibited seizure activity, and flew at terrified residents. Eight people were bitten, but none suffered a related illness. Alfred Hitchcock contacted the newspaper for details. As the story is told, the Hollywood movie producer used the incident as research material for the classic 1963 thriller *The Birds*. About 30 years later it was established that the culprit of this extreme event was an algal bloom of *Pseudo-nitzchia*, select species of which produce domoic acid (DA).[2] DA is a potent neurotoxin that bioaccumulates in filter-feeding shellfish and subsequently enters the food web. DA has been responsible for multiple mass illness and mortality events of shore birds[3] and marine[4–6] and coastal-dwelling mammals,[7] particularly on the U.S. Pacific Coast. These events provided opportunities to capture the naturally occurring physical, physiological, neurologic, cardiac, and behavioral impacts of DA exposure, as well as advance understanding of delayed effects, reexposures, and rehabilitation possibilities.[8,9] Laboratory studies of zebrafish, shellfish, marine mammals, and mice further expanded the capacity for hypothesis testing relevant to protecting public health.[10–12] Nonhuman primate studies, such as that presented by Petroff et al.[8] in this issue of *Environmental Health Perspectives*, represent a unique opportunity to improve understanding of an important contemporary issue: the neural mechanisms underlying chronic exposure to presumably safe levels of DA.

The potential risk of domoic acid to human health was first discovered in Montreal, Canada, in 1987. People who consumed mussels harvested from the Prince Edward Island region with high levels of DA suffered the acute onset of severe gastrointestinal and neurologic symptoms, which in some cases included seizures, coma, and even death.[13,14] Many survivors were left with a permanent anterograde memory disorder, amnesic shellfish poisoning (ASP). Autopsy findings of patients with ASP and early nonhuman primate studies identified damage to the hippocampus as central to seizures and memory problems associated with DA neurotoxicity.[14,15] In the aftermath of this outbreak, extensive research using shellfish, rodent, and nonhuman primate models helped establish current regulatory limits of 20 ppm, ostensibly preventing new cases of ASP.[16–19]

However, the evidence collected over the past decade—which came from epidemiological cohort studies of at-risk Native American communities,[20–22] surveys of recreational and subsistence razor clam harvesters,[23] and risk assessments,[24] combined with zebrafish[25] and rodent,[26,27] models—indicates that repeated, chronic exposure to DA at presumably safe levels (<20 ppm) may have neurotoxic effects impacting many people. Studies of coastal Native American communities with repetitive, low-level exposure for up to 8 y identified the hallmark memory problems associated with ASP in attenuated form.[20,21] Similarly, problems with spatial memory were found in mice exposed to low levels of DA in the absence of other neurologic symptoms.[10] A key finding of this mouse study was the reversibility of the spatial memory problems with exposure cessation, signaling optimism for chronically exposed people.

Petroff et al.[8] conducted many studies in their effort to identify the neural mechanisms of repeated dietary exposure to lower levels of DA upon brain systems, behavior, and adaptation in adult female *Macaca fascicularis* monkeys. The investigators did not find the expected hippocampal excitability in the low-dose monkeys compared with controls. They also did not find differences in hippocampal and thalamic volume connectivity based upon in-life magnetic resonance imaging. What they did find was a "subtle shift" in the molecular profile of the hippocampus, as well as in the microglia phenotype of the thalamus. With appropriate caution, the investigators interpreted this as an adaptive or compensatory response to lower-level DA exposures over time. This could potentially explain the relatively small effect size of memory decline in similarly exposed people. Moreover, it highlights the critical role of the thalamus in the physiological adaptation and recovery of cognitive functions after disruption that have been similarly reported after mild traumatic brain injury.[27] The authors also considered the extent to which these adaptations increase vulnerability to subsequent brain insults, including aging, thus also contributing to the evolving science of brain reserve capacity.[28]

The DA story started with birds and a movie. Along the way, investigative efforts using rodents, fish, marine mammals, wildlife, nonhuman primates, and cohorts of at-risk people complemented, challenged, and advanced science toward the goal of protecting public health. These integrated efforts need to continue toward identifying a simple, reliable biomarker for human exposure assessment; establishing human thresholds for neurotoxicity across the life span; reevaluating current DA regulatory levels for vulnerable populations; further examining the reversibility of chronic exposures; elucidating the interactions of repetitive low-level DA exposure with aging, other exposures, or illnesses; and identifying robust models of community engagement and education.

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The author declares she has nothing to disclose.

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References

1. Trabing W. 1961. Seabird invasion hits coastal homes: thousands of birds floundering in streets. *Santa Cruz Sentinel* 105(195):1. https://history.santacruzpl.org/omeka/items/show/82839#?c=0&m=0&s=0&cv=0 [accessed 21 July 2022].
2. Bargu S, Silver MW, Ohman MD, Benitez-Nelson CR, Garrison DL. 2012. Mystery behind Hitchcock's birds. Nature Geosci 5(1):2–3, https://doi.org/10.1038/ngeo1360.

3. Work TM, Barr B, Beale AM, Fritz L, Quilliam MA, Wright JLC. 1993. Epidemiology of domoic acid poisoning in brown pelicans (*Pelecanus occidentalis*) and Brandt's cormorants (*Phalacrocorax penicillatus*) in California. J Zoo Wildl Med 24(1):54–62. http://www.jstor.org/stable/20460314.
4. Scholin CA, Gulland F, Doucette GJ, Benson S, Busman M, Chavez FP, et al. 2000. Mortality of sea lions along the central California coast linked to a toxic diatom bloom. Nature 403(6765):80–84, PMID: 10638756, https://doi.org/10.1038/47481.
5. Cook PF, Reichmuth C, Rouse AA, Libby LA, Dennison SE, Carmichael OT, et al. 2015. Algal toxin impairs sea lion memory and hippocampal connectivity, with implications for strandings. Science 350(6267):1545–1547, PMID: 26668068, https://doi.org/10.1126/science.aac5675.
6. Greig DJ, Gulland FMD, Kreuder C. 2005. A decade of live California sea lion (Zalophus californianus) strandings along the Central California Coast: causes and trends, 1991–2000. Aquat Mamm 31(1):11–22, https://doi.org/10.1578/AM.31.1.2005.11.
7. Moriarty ME, Tinker MT, Miller MA, Tomoleoni JA, Staedler MM, Fujii JA, et al. 2021. Exposure to domoic acid is an ecological driver of cardiac disease in southern sea otters. Harmful Algae 101:101973, PMID: 33526183, https://doi.org/10.1016/j.hal.2020.101973.
8. Goldstein T, Mazet JAK, Zabka TS, Langlois G, Colegrove KM, Silver M, et al. 2008. Novel symptomatology and changing epidemiology of domoic acid toxicosis in California sea lions (*Zalophus californianus*): an increasing risk to marine mammal health. Proc Biol Sci 275(1632):267–276, PMID: 18006409, https://doi.org/10.1098/rspb.2007.1221.
9. Thomas K, Harvey JT, Goldstein T, Barakos J, Gulland F. 2009. Movement, dive behavior, and survival of California sea lions (*Zalophus californianus*) posttreatment for domoic acid toxicosis. Mar Mamm Sci 26(1):36–52, https://doi.org/10.1111/j.1748-7692.2009.00314.x.
10. Lefebvre KA, Kendrick PS, Ladiges W, Hiolski EM, Ferriss BE, Smith DR, et al. 2017. Chronic low-level exposure to the common seafood toxin domoic acid causes cognitive deficits in mice. Harmful Algae 64:20–29, PMID: 28427569, https://doi.org/10.1016/j.hal.2017.03.003.
11. Gulland FMD, Haulena M, Fauquier D, Langlois G, Lander ME, Zabka T, et al. 2002. Domoic acid toxicity in Californian sea lions (*Zalophus californianus*): clinical signs, treatment and survival. Vet Rec 150(15):475–480, PMID: 11995679, https://doi.org/10.1136/vr.150.15.475.
12. Petroff RL, Williams C, Li JL, MacDonald JW, Bammler TK, Richards T, et al. 2022. Prolonged, low-level exposure to the marine toxin, domoic acid, and measures of neurotoxicity in nonhuman primates. Environ Health Perspect 130(9):097003, https://doi.org/10.1289/EHP10923.
13. Perl TM, Bédard L, Kosatsky T, Hockin JC, Todd EC, Remis RS. 1990. An outbreak of toxic encephalopathy caused by eating mussels contaminated with domoic acid. N Engl J Med 322(25):1775–1780, PMID: 1971709, https://doi.org/10.1056/NEJM199006213222504.
14. Teitelbaum JS, Zatorre RJ, Carpenter S, Gendron D, Evans AC, Gjedde A, et al. 1990. Neurologic sequelae of domoic acid intoxication due to the ingestion of contaminated mussels. N Engl J Med 322(25):1781–1787, PMID: 1971710, https://doi.org/10.1056/NEJM199006213222505.
15. Cendes F, Andermann F, Carpenter S, Zatorre RJ, Cashman NR. 1995. Temporal lobe epilepsy caused by domoic acid intoxication: evidence for glutamate receptor-mediated excitotoxicity in humans. Ann Neurol 37(1):123–126, PMID: 7818246, https://doi.org/10.1002/ana.410370125.
16. Scallet AC, Binienda Z, Caputo FA, Hall S, Paule MG, Rountree RL, et al. 1993. Domoic acid-treated cynomolgus monkeys (*M. fascicularis*): effects of dose on hippocampal neuronal and terminal degeneration. Brain Res 627(2):307–313, PMID: 8298975, https://doi.org/10.1016/0006-8993(93)90335-K.
17. Quilliam MA, Wright JLC. 1989. The amnesic shellfish poisoning mystery. Anal Chem 61(18):1053A–1060A, PMID: 2802153, https://doi.org/10.1021/ac00193a002.
18. Wekell JC, Jurst J, Lefebvre KA. 2004. The origin of the regulatory limits for PSP and ASP toxins in shellfish. J Shellfish Res 23(3):927–930. https://www.researchgate.net/profile/Kathi-Lefebvre/publication/285809374_The_origin_of_the_regulatory_limits_for_PSP_and_ASP_toxins_in_shellfish/links/56c7544908ae5488f0d2cc3a/The-origin-of-the-regulatory-limits-for-PSP-and-ASP-toxins-in-shellfish.pdf.
19. Wright JLC, Boyd RK, de Freitas ASW, Falk M, Foxall RA, Jamieson WD, et al. 1989. Identification of domoic acid, a neuroexcitatory amino acid, in toxic mussels from Eastern Prince Edward Island. Can J Chem 67(3):481–490, https://doi.org/10.1139/v89-075.
20. Grattan LM, Boushey C, Tracy K, Trainer V, Roberts SM, Schluterman N, et al. 2016. The association between razor clam consumption and memory in the CoASTAL cohort. Harmful Algae 57(B):20–25, PMID: 27746706, https://doi.org/10.1016/j.hal.2016.03.011.
21. Grattan LM, Kaddis L, Tracy JK, Morris JG. 2021. Long term memory outcome of repetitive, low-level dietary exposure to domoic acid in Native Americans. Int J Environ Res Public Health 18(8):3955, PMID: 33918677, https://doi.org/10.3390/ijerph18083955.
22. Grattan LM, Boushey CJ, Liang Y, Lefebvre KA, Castellon LJ, Roberts KA, et al. 2018. Repeated dietary exposure to low levels of domoic acid and problems with everyday memory: research to public health outreach. Toxins (Basel) 10(3):103, PMID: 29495583, https://doi.org/10.3390/toxins10030103.
23. Ferriss BE, Marcinek DJ, Ayres D, Borchert J, Lefebvre KA. 2017. Acute and chronic dietary exposure to domoic acid in recreational harvesters: a survey of shellfish consumption behavior. Environ Int 101:70–79, PMID: 28109640, https://doi.org/10.1016/j.envint.2017.01.006.
24. Stuchal LD, Grattan LM, Portier KM, Kilmon KA, Manahan LM, Roberts SM, et al. 2020. Dose-response assessment for impaired memory from chronic exposure to domoic acid among Native American consumers of razor clams. Regul Toxicol Pharmacol 117:104759, PMID: 32768666, https://doi.org/10.1016/j.yrtph.2020.104759.
25. Lefebvre KA, Tilton SC, Bammler TK, Beyer RP, Srinouanprachan S, Stapleton PL, et al. 2009. Gene expression profiles in zebrafish brain after acute exposure to domoic acid at symptomatic and asymptomatic doses. Toxicol Sci 107(1):65–77, PMID: 18936300, https://doi.org/10.1093/toxsci/kfn207.
26. Sobotka TJ, Brown R, Quander DY, Jackson R, Smith M, Long SA, et al. 1996. Domoic acid: neurobehavioral and neurohistological effects of low-dose exposure in adult rats. Neurotoxicol Teratol 18(6):659–670, PMID: 8947943, https://doi.org/10.1016/S0892-0362(96)00120-1.
27. Munivenkatappa A, Devi BI, Shukla DP, Rajeswaran J. 2016. Role of the thalamus in natural recovery of cognitive impairment in patients with mild traumatic brain injury. Brain Inj 30(4):388–392, PMID: 26619364, https://doi.org/10.3109/02699052.2015.1089599.
28. Stern Y, Barnes CA, Grady C, Jones RN, Raz N. 2019. Brain reserve, cognitive reserve, compensation, and maintenance: operationalization, validity, and mechanisms of cognitive resilience. Neurobiol Aging 83:124–129, PMID: 31732015, https://doi.org/10.1016/j.neurobiolaging.2019.03.022.