ALGAL TOXICOSIS

AETIOLOGY

Classification of the causative agent

Because the term “algal toxicosis” encompasses a significant number of toxic agents, this technical card will focus on specific toxins most relevant to wildlife species.

While the term “algae” encompasses a wide range of species, this technical card will focus on harmful algal blooms (HABs) that produce toxins causing clinical signs in animals. HABs are defined as excessive growth of algal species that produce toxins in aquatic environments. These algal species include diatoms, dinoflagellates, and cyanobacteria (blue-green algae, class *Cyanophyceae*), with the latter being the most common and dangerous to wildlife species. Algae may proliferate due to excessive phosphorus or nitrogen in the water or may be transported to new environments by ships or hurricanes. Birds suffer the most from mass mortality events due to toxicoses.

Cyanobacteria live in fresh, brackish, or marine water; the majority of dinoflagellates thrive in marine environments, whereas diatoms may live in either marine or freshwater ecosystems. Cyanobacteria are classified as prokaryotic, photosynthetic organisms that produce chlorophyll-a. Dinoflagellates are eukaryotic, unicellular organisms with a pair of flagella; the majority of these organisms are photosynthetic. Diatoms are unicellular marine algae enveloped in silica.

This technical card will focus on: anatoxins, β-N-methylamino-1-alanine (BMAA), and microcystins, produced by several species of cyanobacteria; brevetoxins and saxitoxins (STX), produced by dinoflagellates; and domoic acid (DA), produced by diatoms.

Resistance to physical and chemical action

Temperature: Depending on the species, algae can grow in temperatures ranging from 4-15°C

pH: Harmful algal blooms proliferate at high pH

Chemicals/Disinfectants: Copper sulfate ($CuSO_4$) or other algicidal copper-based compounds can effectively remove cyanobacteria from water at concentrations of 0.2-0.4 ppm

Survival: Algae survives under warm environmental conditions, high atmospheric CO_2 concentrations, and low salinity

EPIDEMIOLOGY

Affected Species

Because algal toxins are capable of affecting numerous species, the term “affected species” as used in this technical card will refer to species for which these compounds are currently an appreciable danger. It should be noted that there may be variability in species’ relevance due to inherent differences in species sensitivity, environmental differences, anthropogenic factors, route of exposure, et cetera.

Anatoxins are made by *Aphanizomenon*, *Anabaena*, and *Planktothrix* cyanobacteria; brevetoxins are produced by *Gymnodinium* or *Karenia* spp.; domoic acid is produced by the diatom *Pseudo-nitzschia* spp.; microcystins are produced by *Microcystis*, *Anabaena*, *Planktothrix* and *Nostoc* cyanobacterial species; and

saxitoxins are made by the cyanobacteria *Aphanizomenon*, *Anabaena,* and *Lyngba,* and the dinoflagellate *Alexandrium* spp. These toxins cause pathology in a number of domestic livestock, marine mammals, reptiles, and waterfowl throughout the world. The following list is not exhaustive, therefore not all host species or toxins will be discussed.

Anatoxins

- Greater flamingos (*Phoenicopterus ruber*)

β-N-methylamino-1-alanine (BMAA)

- Aquatic birds
    - American coots (*Fulica americana*)
    - Buffleheads (*Bucephala albeola*)
    - Mallards (*Anas platyrhyncos*)
- Bald eagles (*Haliaeetus leucocephalus*)
- Several fish species
    - European smelt (*Osmerus eperlanus*)
    - Turbot (*Scophthalmos maximus*)
- Mollusks
    - Blue mussel (*Mytilus edulis*)
    - European flat oyster (*Ostrea edulis*)

Brevetoxins

- Bottlenose dolphins (*Tursiops* spp.)
- Double-crested cormorants (*Phalacrocorax auritus*)
- Lesser scaups (*Aythya affinis*)
- Manatees (*Trichechus manatus*)

Domoic acid (DA)

- Brandt's cormorants (*Phalacrocorax penicillatus*)
- Brown pelicans (*Pelecanus occidentalis*)
- California sea lions (*Zalophus californianus*)
- Lesser scaup (*Aythya affinis*)
- Southern sea otters (*Enhydra lutris nereis*)

Microcystin

- White rhinoceroses (*Ceratotherium simum*)

Saxitoxins (STX)

- Atlantic mackerel (*Scomber scombrus*)
- Baleen whales (*Mysticeti* spp.)
- Bottlenose dolphin (*Tursiops truncatus*)
- Green turtles (*Chelonia mydas*) and olive ridley turtles (*Lepidochelys olivacea*)
- Humpback whales (*Megaptera novaeangliae*)
- Mediterranean monk seals (*Monachus monachus*)
- Puffer fishes (*Sphoeroides* spp.)
- Right whales (*Eubalaena glacialis*)

Routes of Exposure

- Toxicosis may occur due to consumption of fish and invertebrates (molluscs, zooplankton) that have bioaccumulated toxins
- Drinking contaminated water from lakes, ponds, dams, or puddles
- Inhalation of aerosolized toxins

Sources

- Fish and invertebrates
- Contaminated water
- Aerosolized toxins

Occurrence

Toxins may occur anywhere in the world and are brought on by warm, sunny weather and increased water temperatures. These blooms can be incited by fertiliser, soap, and waste run-off consisting of nitrogen and phosphorus. Wind may lead to the accumulation of algae in water along shorelines where it is easy for animals to access drinking water. Ruminants and birds are more negatively affected by toxic algae ingestion than monogastric animals. Cyanobacterial algal blooms are blue-green in colour; red tides events are generally reddish-brown.

Anatoxins

Anatoxins are neurotoxic alkaloids produced by cyanobacteria and have contributed to several mass mortality events in wild avian species. An event in a Danish freshwater lake was due to *Anabaena* cyanobacterial blooms. Events in Spain have occurred in Doñana National Park, including an *Anabaena flos-aquae* bloom that caused the death of greater flamingos.

β-N-methylamino-1-alanine (BMAA)

BMAA is an amino acid made by all cyanobacteria. It often occurs in the southeastern United States in late autumn to early winter. It primarily affects bald eagles (*Haliaeetus leucocephalus*) and can bioaccumulate in fish.

Brevetoxins

These polyether toxins are produced by the dinoflagellates *Karenia brevis* and *Gymnodinium breve*; these two dinoflagellate species also contribute to annual red tide events in Florida, United States. Algal blooms off the Florida coast usually reach land by fall and winter, though sometimes appear in the spring, and can last several months. Off the coast of Japan, red tides are due to raphidophytes of the *Chattonella* genus. Finfish experience severe clinical signs of *K. brevis* toxicosis. Other species that experience heavy die-offs during these algal blooms include: cormorants, lesser scaups, bottlenose dolphins, and manatees.

Domoic Acid (DA)

DA is a neurotoxin predominantly produced by diatoms. A *Pseudo-nitzschia australis* diatom bloom off the central coast of California corresponded with DA poisonings in California sea lions. Southern sea otters have also been affected by DA poisoning. Sea birds that have experienced DA toxicosis include lesser scaup, Brandt's cormorants, and brown pelicans.

Microcystin

Microcystin toxins are hepatotoxic heptapeptides predominantly occurring in freshwater and are produced by several cyanobacteria including *Microcystis* and *Anabaena* spp. Algal bloom toxicosis events due to *Microcystis* spp. have killed white rhinoceroses in Kruger National Park, South Africa. These occur after dry summers and warm autumns in bodies of water with little water and lots of organic matter. A *Microcystis aeruginosa* bloom in the park also caused deaths of at least 6,000 birds from 47 species.

Saxitoxins (STXs)

STXs are neurotoxins that can be produced by several cyanobacterial and dinoflagellate species, including *Anabaena*, *Alexandrium*, and *Pyrodinium* spp. A number of mass mortality events are thought to have occurred due to STX exposure, though not all can be confirmed. STXs produced by dinoflagellate *Alexandrium tamarense* are thought to have caused death in humpback whales off the coast of Massachusetts, United States. Baleen whales had undigested Atlantic mackerel in their stomachs, cited as a potential source of STX exposure and therefore death. Another STX-related death was thought to occur off the Mauritanian coast in Mediterranean monk seals. It is thought that accumulated STX from *Alexandrium fundyense* in shellfish eaten by right whales contributed to the reduced breeding rate of this marine species in the North Atlantic ocean. A

bottlenose dolphin mortality event occurred in the Indian River Lagoon in Florida, United States possibly due to STX ingestion from puffer fish. In this area, STX was made by the *Pyrodinium bahamense* var. *bahamense* and accumulated within puffer fish. Large die-offs of green and olive ridley turtles in 2013 and 2017 took place off the coast of El Salvador. Specifically, these die-offs were thought to be due to *Alexandrium* spp., *Gymnodinium catenatum*, and *Pyrodinium bahamense* var. *compressum*.

For more recent, detailed information on the occurrence of these diseases worldwide, see the OIE World Animal Health Information System - Wild (WAHIS-Wild) Interface [http://www.oie.int/wahis_2/public/wahidwild.php/Index].

DIAGNOSIS

Anatoxins

Toxins produced by cyanobacteria are released from algal cells after being destroyed by animal's stomach acids or by cyanobacterial cell autolysis. These are absorbed by the intestinal tract and are metabolised by the liver. Though the neurotoxin's pharmacology is not well-described, it is thought that anatoxins act as acetylcholinesterase (AChE) inhibitors and cause accumulation of acetylcholine (ACh) in neuromuscular junctions, resulting in neuromuscular blockage and respiratory arrest.

β-N-methylamino-1-alanine (BMAA)

This amino acid (BMAA) primarily affects neurons. It can form β-carbamate, which functions as a glutamate receptor agonist, and causes excitotoxicity with subsequent neurological cell impairment. BMAA may also bind proteins, causing neuronal apoptosis.

Brevetoxins

Brevetoxins bind to site 5 on voltage-gated sodium channels, thereby prohibiting the channel from closing.

Domoic Acid (DA)

DA is a water-soluble amino acid made by diatoms in the *Pseudo-nitzschia* genus. It acts as a glutamate neurotransmitter.

Microcystin

Microcystins are absorbed via the respiratory system. In the liver, microcystins inhibit protein phosphatases 1 and 2A; this causes actin filament changes and damage to the hepatocyte cytoskeleton and sinusoidal endothelium.

Saxitoxin (STX)

These cause toxicity by blocking voltage-gated sodium channels.

Clinical diagnosis

Anatoxins

Signs of anatoxin-a and homoanatoxin-a neurotoxicosis include muscle tremor, cyanosis, paralysis, rigidity, and opisthotonos (in birds). Signs of anatoxin-a(s) ("s" indicates "salivation") ingestion include excessive salivation, urinary incontinence, and lacrimation.

Clinical signs of *Gymnodinium breve* toxicosis in birds include hypothermia, flightlessness, head drooping, weakness, lacrimation, oral and nasal discharge, dyspnoea, tachypnoea, chalky yellow diarrhoea, and dehydration. *Anabaena flos-aquae* toxicosis in waterfowl causes opisthotonos, convulsions, repeated swallowing and salivation, restlessness, and death.

β-N-methylamino-1-alanine (BMAA)

This toxin is thought to cause avian vacuolar myelinopathy (AVM). BMAA toxicosis in birds causes clinical signs after about 1 week post-exposure; these signs include ataxia, inability to walk or fly, weakness, tilting, and death.

Brevetoxins

Manatees affected by these toxins experience listlessness, laboured breathing, disorientation, and inability to submerge or maintain a horizontal position.

Domoic Acid (DA)

California sea lions poisoned by DA develop ataxia, seizures, scratching, and disorientation. Other signs include premature births, abortion, or maternal mortality. If sea lions survive, they may experience neurological sequelae such as persistent seizures that can increase their risk of being stranded on land. Seal pups exposed *in utero* may have epilepsy or neurological deficits. Birds exposed to DA may experience vomiting, weakness, oculonasal and oral discharge, head drooping, and side-to-side head movements.

Microcystin

Microcystin hepatotoxicosis causes acute death within a few hours of algae ingestion. Clinical signs include shock, diarrhoea, pallor, general weakness, and vomiting. If animals survive the first few hours post-exposure, hyperkalaemia, nervousness, recumbency, convulsions, or hypoglycaemia may occur.

Saxitoxin (STX)

These toxins cause respiratory arrest, vomiting, paralysis, miosis, intestinal haemorrhage, and death.

Lesions

- Anatoxins
    - No gross or microscopic lesions present
- Birds (AVM) due to β-N-methylamino-1-alanine (BMAA)
    - Histologic lesions not always present
    - Bilateral vacuolisation of white matter in central nervous system
- Domoic acid (DA)
    - California sea lions and southern sea otters
        - Fibrinous pericarditis
        - Myocardial pallor
    - California sea lions
        - Hippocampal atrophy
        - Ischemic neuronal necrosis
- Microcystins
    - Hepatomegaly
    - Progressive centrilobular hepatocyte rounding, dissociation, and necrosis
- Saxitoxins (STX)
    - No significant histological lesions

Differential diagnoses

- Birds
    - Botulism
- Hepatotoxicity secondary to ingestion of:
    - Acetaminophen
    - Aflatoxin
    - Amanitins
    - Cocklebur
    - Cycad palm
    - Heavy metals
    - Xylitol
- Neurotoxicosis
    - Rabies
    - Morbilliviruses
    - Hepatic encephalopathy

Laboratory diagnosis

Samples

For isolation of agent

- Algal/water samples
- Kidney
- Liver
- Stomach contents
- Blood
- Urine

Serological tests

- Serology is not used to detect algal toxicoses.

Procedures

Identification of the agent

- Algae or dinoflagellate identification can help narrow down the toxin to which an animal was exposed
- A receptor-binding assay colorimetric plate is available for the detection of anatoxin-a in water
- Microcystin detection in water
    - High-performance liquid chromatography (HPLC)
    - Mass spectrometry
- Electrospray ionization liquid chromatography-mass spectrometry
    - Provides bound microcystin concentrations in tissues
- Commercial enzyme-linked immunosorbent assay (ELISA) kits are available for the detection of saxitoxins and microcystins in water
- Competitive ELISAs may be used for the detection of brevetoxins, DA, and saxitoxins in animal tissues
- Neuroreceptor assays are available to detect saxitoxin in blood and urine
- BMAA may be detected in fish tissues using toxin extraction and hydrophilic interaction liquid chromatography with tandem mass spectrometry analysis (HILIC-MS/MS), though this is more commonly used in research settings
- There are no recommended methods to detect anatoxins in tissues

Serological tests

- Serology is not used to detect algal toxicoses.

PREVENTION AND CONTROL

Sanitary prophylaxis

- Apply algicides and clear water of surface scum in ponds or lakes prone to algal blooms
    - Take caution when breaking up algal mats or administering algicides, as doing so may cause toxin release into the water
    - Water can be treated with ozone or chlorine; however, it is important to also treat the water with a compound that can dissolve cyanotoxins released by the bacteria
        - Microcystins are also oxidized by ozone and chlorine
    - Copper sulfate ($CuSO_4$) or other algicidal copper-based compounds can effectively remove cyanobacteria from water at concentrations of 0.2-0.4 ppm
    - Microcystins, saxitoxins, and anatoxin-a can be adsorbed by granular and activated powdered carbon
- Regarding nitrogen and phosphorus:
    - Monitor agricultural use of fertilisers, especially nitrogen and phosphorous compounds; divert agricultural run-off away from popular wildlife or livestock watering holes
    - Compounds that bind and remove phosphorus from water include ferric chloride, aluminium sulfate, alum (potassium aluminium sulfate), lime, and clay particles
- Wear rubber or latex gloves when handling animals affected by algal toxins
- Remove animals from water sources with harmful algal blooms
- Monitor at-risk populations of animals (e.g. bottlenose dolphins) for risk of intoxication

Medical prophylaxis

- There are no vaccines available against toxins produced by algae, diatoms, or dinoflagellates.
- Cyclosporine A, glutathione, silymarin, and antioxidants can decrease microcystin toxicity in animals if given prophylactically.
- If an animal is suspected to have experienced algal toxicosis, provide it with fresh water and food and move it out of the sun. Provide it with an activated charcoal slurry.
    - Atropine and activated charcoal can decrease the muscarinic response to anatoxin-a(s).

POTENTIAL IMPACTS OF DISEASE AGENT BEYOND CLINICAL ILLNESS

Risks to public health

- Bioaccumulation due to ingestion of shellfish can cause paralytic shellfish poisoning (saxitoxins), neurotoxic shellfish poisoning (brevetoxins), and amnesic shellfish poisoning (domoic acid).
- BMAA can cause motor neuron destruction in the brain to yield neurodegenerative diseases like lathyrism and amyotrophic lateral sclerosis-parkinsonism-dementia complex of Guam (Guam ALS-PD).
- Blue-green algal dietary supplements may put people at increased risk of consuming anatoxins.

Risks to agriculture

- Livestock are at risk of algal toxicosis if they have access to water sources prone to algal blooms, such as ponds.
- Fish, shellfish, and other farmed animals may become ill or die due to algal toxicosis, resulting in significant economic losses for farmers.

REFERENCES AND OTHER INFORMATION

- Al-Sammak, M. A., Hoagland, K. D., Cassada, D., & Snow, D. D. (2014). Co-occurrence of the cyanotoxins BMAA, DABA, and anatoxin-α in Nebraska reservoirs, fish, and aquatic plants. *Toxins*, *6*, 488-508.

- Amaya, O., Quintanilla, R., Stacy, B. A., Dechraoui Bottein, M., et al. (2018). Large-scale sea turtle mortality events in El Salvador attributed to paralytic shellfish toxin-producing algae blooms. *Frontiers in Marine Science*, *5*(411), 1-10.
- Carmichael, W. W. (2013). Overview of algal poisoning. *Merck Veterinary Manual*. Accessed 2020: https://www.merckvetmanual.com/toxicology/algal-poisoning/overview-of-algal-poisoning?query=algal%20poisoning
- Degernes, L. A. (2008). Waterfowl toxicology: A review. *Veterinary Clinics: Exotic Animal Practice*, *11*, 283-300.
- Fire, S. E & Van Dolah, F. M. (2012). Marine biotoxins: Emergence of harmful algal blooms as health threats to marine wildlife. In A. A. Aguirre, R. S. Ostfield, and P. Paszak (Eds.), *New Directions in Conservation Medicine: Applied Cases in Ecological Health* (pp. 375-383). New York: Oxford University Press,
- Fryxell, G. A. & Hasle, G. R. (2003). Chapter 17: Taxonomy of harmful diatoms. In G. M. Hallegraeff, D. M. Anderson, and A. D. Cembella (Eds.), *Manual on Harmful Marine Microalgae* (2nd ed., p. 465). United Nations Educational, Scientific, and Cultural Organization.
- Handeland, K. & Gavier-Widén, D. (2012). Chapter 41: Harmful algal blooms including cyanobacterium toxicosis. In D. Gavier-Widén, J. P. Duff, and A. Meredith (Eds.), *Infectious Diseases of Wild Mammals and Birds in Europe* (pp. 476-480). Blackwell Publishing Ltd.
- Landsberg, J. H., Vargo, G. A., Flewelling, L. J., & Wiley, F. E. (2007). Algal biotoxins. In N. J. Thomas, D. B. Hunter, and C. T. Atkinson (Eds.), *Infectious Diseases of Wild Birds* (pp. 431, 446). Blackwell Publishing.
- Main, B. J., Bowling, L. C. Padula, M. P., Bishop, D. P., et al. (2018). Detection of the suspected neurotoxin β-methylamino-L-alanine (BMAA) in cyanobacterial blooms from multiple water bodies in Eastern Australia. *Harmful Algae*, *74*, 10-18.
- Miller, M. A., & Buss, P. E. (2015). Rhinoceridae (Rhinoceroses). In R. E. Miller and M. E. Fowler, *Fowler's Zoo and Wild Animal Medicine* (Vol. 8, p. 544). Elsevier.
- Puschner, B. (2018). Cyanobacterial (blue-green algae) toxins. In R. C. Gupta (Ed.), *Veterinary Toxicology: Basics and Principles* (3rd ed., pp. 764, 770-772). Academic Press.
- Rocke, T. E., & Friend, M. (1999). Biotoxins. In M. Friend, J. C. Franson, and E. A. Ciganovich (Eds.), *Field Manual of Wildlife Diseases* (pp. 264-266). USGS.
- Taylor, F. J. R., Fukuyo, Y., Larsen, J., & Hallegraeff, G. M. (2003). Chapter 15: Taxonomy of harmful dinoflagellates. In G. M. Hallegraeff, D. M. Anderson, and A. D. Cembella (Eds.), *Manual on Harmful Marine Microalgae* (2nd ed., p. 389). United Nations Educational, Scientific, and Cultural Organization.
- Visser, P. M., Verspagen, J. M. H., Sandrini, G., Stal, L. J., et al. (2016). How rising CO_2 and global warming may stimulate harmful cyanobacterial blooms. *Harmful Algae*, *54*, 145-159.
- Wang, S., Qiu, J., Zhao, M., Li, F., Yu, R., & Li, A. (2020). Accumulation and distribution of neurotoxin BMAA aquatic animals and effect on the behavior of zebrafish in a T-maze test. *Toxicon*, *173*, 39-47.
- Wiley, F. E., Wilde, S. B., Birrenkott, A. H., Murphy, S. K., et al. (2007). Investigation of the link between Avian Vacuolar Myelinopathy and a novel species of cyanobacteria through laboratory feeding trials. *Journal of Wildlife Diseases*, *43*(3), 337-344.

*
* *

The OIE will periodically update the OIE Technical Disease Cards. Please send relevant new references and proposed modifications to the OIE Science Department (scientific.dept@oie.int). Last updated 2020. Written by Samantha Gieger and Erin Furmaga with assistance from the USGS National Wildlife Health Center.