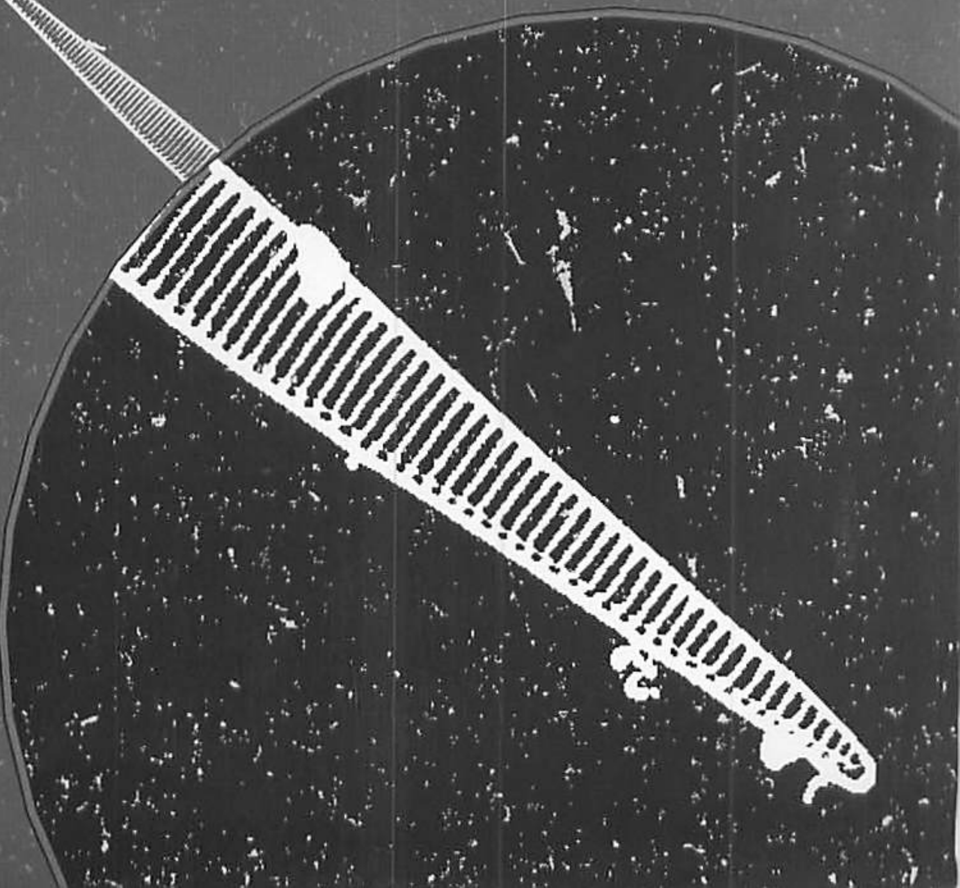
DOMOIC ACID

Final Report of the Workshop

Oregon Institute of Marine Biology
February 21-23, 1992



Edited by A. Michelle Wood
and Lynda M. Shapiro

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THE WORKSHOP REPORT

Introduction

Amnesic shellfish poisoning (ASP) is a recently identified threat to the seafood consuming public. It is caused by the neurotoxin domoic acid, which can be concentrated by filter-feeding shellfish as they consume smaller organisms that produce the toxin. The first incidence of a human disease caused by domoic acid in shellfish was documented in 1987 on Prince Edward Island in eastern Canada. Scientists there identified the causative organism and helped develop a successful management strategy. This has allowed the shellfish industry there to continue to grow, and its harvest of cultured mussels there now exceeds 1987 levels. Despite the continued annual appearance of the diatom that produces domoic acid, tainted products have been kept off the market and public confidence in the Prince Edward Island mussel industry is high. This regional success story suggests that the domoic acid problems that emerged on the west coast of the United States in the fall of 1991 can be managed equally well.

The west coast incident started with the deaths of pelicans and cormorants in Monterey Bay in September 1991. Extensive testing ruled out pollutants, pesticides, bacteria, viruses, and heavy metals, but the behavior of mice being tested for possible paralytic shellfish poisoning (PSP) indicated that domoic acid was present in the birds. In late October, domoic acid was discovered in razor clams from the surf zone of Oregon and Washington coastal beaches, causing the closure of both the commercial and recreational fisheries. By early December, Dungeness crabs in California, Oregon, and Washington were found to contain the toxin, and that fishery was also closed. However, other clam species, mussels, and oysters never became toxic.

In response to these events, Sea Grant sponsored a workshop on domoic acid at the University of Oregon's Institute of Marine Biology, February 20–23, 1992. The principal purpose was to identify scientific issues that must be addressed in order to achieve a successful management program. We recognize that a new public health threat of this type involves both an immediate, emergency response and a longer-term response. Closures and enhanced monitoring of the fisheries were some of the immediate responses. Our goal at the February meeting was to consider longer-term responses.

Participants at the workshop included some scientists who have studied problems related to domoic acid since the first outbreaks in Canada and many west coast scientists who have been part of the immediate response efforts in California, Washington, and Oregon. Among them were experts in toxic phytoplankton, domoic acid–producing phytoplankton, phytoplankton ecology, shellfish biology, molecular biology, and physical oceanography, as well as representatives from government agencies and industry. (See Appendix 1 for a list of participants and their affiliations.)

The participants identified three scientific priorities for a research plan that will provide the information needed to develop an optimal strategy for managing domoic acid. First, we need to determine the source of domoic acid and the mechanisms by which it accumulates in shellfish and other organisms. While workshop participants recommended continued focus on diatoms in the *Nitzschia/Pseudonitzschia* complex as the most likely source of domoic acid, sufficient differences exist between the domoic acid outbreaks in California, Oregon-Washington, and Canada to require considering the possibility that the source of domoic acid differs in all three areas.

Second, there is an amazingly small body of basic ecological information about phytoplankton dynamics off the Pacific Northwest coast. Process-oriented studies, which condensed information on phytoplankton into taxa-insensitive measures such as chlorophyll concentration and rate of total primary production, have dominated oceanographic research off the northwest Pacific coast for some time. As a result, we have little information on phytoplankton species composition and on processes determining the abundance and distribution of species in coastal waters. Responses to the domoic acid problem and to other nuisance phytoplankton taxa that may arise in the future require an immediate and sustained effort to obtain this information. Further, the work must proceed on ecologically meaningful spatial and temporal scales despite the fact that individual states have different fisheries priorities and different mechanisms for supporting the research. Because the California Current links ecologically similar coastal environments from southern Alaska to Monterey Bay, investigation of phytoplankton species distribution and population dynamics must consider this regional ecosystem as well as local subsystems.

Third, all working groups recognized the need for a straightforward assay for domoic acid that can be applied to tissue samples as well as to water and sediment samples. An assay that could reliably, inexpensively, and rapidly indicate the presence of domoic acid at low levels and provide rough estimates of concentration at higher levels would be of tremendous value for both monitoring and research applications, even if it lacked the precision of HPLC-based methods.

Additionally, the participants recognized the need for training in methods of detection and standardization of detection methods throughout the affected area.

During the second day of the workshop, we met in working groups to draft research recommendations. The three working groups were (1) Phytoplankton, (2) Public Health and Detection, and (3) Shellfish. The separate reports of the working groups follow. Where the separate groups arrived at identical recommendations, we have allowed the redundancy to remain because the emphasis it conveys reflects the consensus of the participants.

Report of the Phytoplankton Working Group

Peter Franks (Oregon State University), Greta Fryxell (Texas A&M University), Lynda Shapiro (University of Oregon), and Michelle Wood (University of Oregon)

Working groups discussed phytoplankton ecology in the morning session and phytoplankton culture studies during the afternoon session. The results of these deliberations have been integrated and are presented below.

It is generally agreed that the question with highest priority is, What organisms are the source of domoic acid? This question must be answered before other high priority questions concerning the ecophysiology of domoic acid production and the ecology of the blooms can be addressed.

In eastern Canada, where clear cases of amnesic shellfish poisoning were documented in people who had eaten domoic acid–containing mussels, researchers have established that the causative organism is a form of the chain-forming diatom *Nitzschia pungens* (forma *multiseries*). In this taxon, studies with unialgal cultures indicate that domoic acid production increases with increasing senescence; nitrate and light appear to be necessary for domoic acid production, with cell growth limited by some other factor. Toxicity of isolates appears to decrease as the cells are maintained in culture for longer than a year, and some preliminary data show that levels of domoic acid production decrease in axenic culture relative to that of unialgal cultures that are not bacteria-free.

In Monterey Bay, no human health effects were observed, but pelican mortality was traced to the ingestion of anchovies that had been feeding on the chain-forming diatom *Pseudonitzschia australis*, the dominant member of the phytoplankton community at the time. Preliminary data from studies with unialgal (but not bacteria-free) cultures of *P. australis* indicate that this organism produces domoic acid. Research on *P. australis* is obviously more limited than research on *N. pungens* forma *multiseries* since its possible role as a toxic agent was not suspected until fall 1991.

The Monterey Bay pelican kill is, to date, the only example of transmission of toxic levels of domoic acid to vertebrates through a plankti-vorous fish vector.

Finally, in Oregon and Washington, where mild cases of neurologic disorder and gastric distress in humans have been traced to consumption of razor clams containing domoic acid, data on the phytoplankton species composition at the time of harvest are unavailable. However, *P. australis*, and *N. pungens* cells, with morphologies that conform to species descriptions for both the toxic and nontoxic form, have been obtained in phytoplankton samples collected from the region after the detection of domoic acid in shellfish. These taxa did not dominate the phytoplankton community, even at sites where the domoic acid concentration in razor clam tissue continued to increase. (This is a common feature of many nuisance blooms.)

Field and laboratory studies, as well as common sense, argue strongly that phytoplankton, probably *N. pungens* f. *multiseries*, *P. australis*, or close relatives, are the sources of domoic acid in fish and shellfish on the west coast of the United States. Because of the potential economic and human health problems associated with shellfish that has been contaminated with domoic acid, research on the environmental factors that control domoic acid production in *Nitzschia* and *Pseudonitzschia* species should be given high priority.

The differences between health and food chain effects observed in California, Washington-Oregon, and eastern Canada make it necessary to consider simultaneously the possibility that other organisms, either singly or in addition to *N. pungens* and *P. australis*, are responsible for the presence of domoic acid in shellfish and anchovies. In particular, other *Nitzschia* species, that is *N. delicatula* and *N. pseudodelicatisima*, may be capable of domoic acid production. It is important to examine dominant members of the surf zone phytoplankton community, epiphytes on kelp and eelgrass, and decaying beach wrack as potential sources of domoic acid. The diatom *Amphora coffeaeformis* is a suspected producer of domoic acid, and it may be part of the epiphyte community. Both its presence and its toxicity should be confirmed. Also the red alga *Chondria armata*, thought to be a relatively rare taxon on the Washington-Oregon coast, produces domoic acid and therefore deserves some additional study of its distribution and abundance. It should be noted that the affected shellfish in Washington and Oregon coastal waters live in more exposed environments than Monterey Bay or the embayments of Prince Edward Island.

As organisms that produce domoic acid are identified, the following questions take on the highest priority :

1. What factors govern domoic acid production?
2. What is the life history of each organism that produces domoic acid, and are there particular life history stages involved in domoic acid production or particular life history stages that can be exploited in a management program?
3. What is the physical ecology of population increases (for example, blooms) of the domoic acid–producing species?

Studies of the physical ecology of blooms of domoic acid–producing species must consider a number of topics: the environmental factors that govern species abundance and toxin production; the regularity, both temporal and spatial, of blooms of domoic acid–producing species; and the heterogeneity of the bloom community. Also, it is possible that the domoic acid–producing taxa have been introduced by human activities such as shipping; this possibility and its implications should be considered. A critical aspect of much of this work will be the identification of known domoic acid producers in field samples containing a large number of species. This is likely to be a difficult and time-consuming task. Therefore, we suggest that an effort be made to develop genetic probes that will distinguish between species in the field. In addition, an inexpensive and rapid domoic acid assay would allow easy identification of toxic waters.

The most fundamental aspect of bloom studies will be the development of a good sampling program. It is imperative that we understand the geographic scope of domoic acid outbreaks and the temporal range in which they occur. We must gain knowledge of the organism's life history to understand its distribution alongshore and offshore, the factors leading to domoic acid production, and the mechanisms of delivery to the amnesic shellfish poisoning vectors (for example, anchovy, razor clams, crabs, mussels). The plankton sampling must be integrated with hydrographic sampling (temperature, salinity and nutrient profiles at a minimum, also *in situ* fluorescence, beam transmittance, and currents). The studies should also consider historical data to examine environmental forcing of domoic acid outbreaks. Field studies should span a wide geographic area (southern California to northern Washington at minimum, but preferably including British Columbia and Alaska) to compare and seek links between adjacent outbreaks. Temporal coverage should be fine enough to identify the initiation of toxic outbreaks so that a sequence of events can be identified.

Laboratory work should examine the biochemical and genetic aspects of domoic acid production, the phylogenetic relationships of domoic acid–producing species, and particularly, the responses of these species to a variety of environmental stresses—for example, nutrient and light limitation and temperature effects. These experiments should also consider the role of other organisms (for example, bacteria) in domoic acid production and work toward understanding the genetic basis for the biosynthesis of domoic acid.

Finally, we must gain more knowledge of the vectors of domoic acid transmission. In particular, what can the feeding ecology of these organisms tell us about the toxic blooms? How is domoic acid distributed throughout the food web? And can these organisms take up dissolved domoic acid as opposed to actually ingesting toxic cells?

To better understand the dynamics of domoic acid outbreaks, the group identified special needs:

1. Sampling schemes that provide temporal or spatial surveys of plankton and hydrography
2. Establishment of additional new cultures of both toxic and nontoxic species.
3. More extensive culture studies
4. A "quick-and-dirty" assay for domoic acid
5. Elucidation of the biochemical pathway and genetic components leading to domoic acid production
6. Field studies of domoic acid "hot spots"
7. Preservation of field samples and subsequent gut analysis where appropriate

The working groups gave high priority to a recommendation for the establishment of an integrated sampling program for toxic algal blooms, including those producing paralytic shellfish poisoning, amnesic shellfish poisoning, and diarrhetic shellfish poisoning. This sampling program ideally would span from southern California to Alaska, including the coast of British Columbia. It is likely that novel toxic outbreaks will continue to occur. Such a sampling program will create a sample archive that would provide necessary information to researchers trying to understand the courses of events, and could aid in a fast, coordinated effort at protecting the public and the shellfish industry from harm.

Report of the Public Health and Detection Working Group

Bill Keene (Oregon Health Division) and John Wekell (National Marine Fisheries Service)

Overview of Monitoring Needs

1) There is an immediate need to protect consumers from the danger of acute illness and simultaneously to allow seafood to move commercially without (undue) hindrance, that is, by certifying it as "safe" (or at least as being below some recognized action level of contamination).

2) There is also a need for more research-oriented programs, designed to more efficiently or more sensitively predict and detect domoic acid

occurrences. A better understanding of the underlying phenomena will also improve planning capabilities of public health officials and of industry and consumers.

Routine Monitoring

Although these components need not be completely independent, it should be understood that a preliminary monitoring program is already in place, albeit in an ad hoc manner, and it is rapidly evolving under the aegis of the FDA and the respective state shellfish programs to become a routine program that will be managed by the states.

There are few significant variations among the several draft monitoring programs on the table in Washington, Oregon, and California. They are wholly analogous to pre-existing PSP programs, consisting of

a. routine collection of commercially and (to a lesser extent) recreationally important species, especially oysters, mussels, clams, and crab, consumed by humans
b. HPLC sampling of specimens for domoic acid by FDA, state, or other laboratories
c. dissemination of results to interested parties, with regulatory action taken as levels reach (or approach) 20 ppm
d. intensified monitoring activities as levels begin to rise significantly ("significant" to be defined later, but presumably at inflection points on any domoic acid level vs. time plot, for example, a shift from zero to 2–5 ppm)

These routine monitoring programs will be a reasonable source of baseline data (on those species in sampled areas, at least), but efforts to develop alternative monitoring programs should be designed as stand-alone scientific projects.

Research Needs for Domoic Acid Monitoring

Research efforts should concentrate on identifying and evaluating potential invertebrate and vertebrate indicator species or environmental conditions that might be cheaper or better than the "brute force" method of testing food before people eat it. Seasonality or other cyclic phenomena may be important aspects of domoic acid occurrence and should be a focus of attention in all spheres of research.

To identify indicator species, we must begin with a broad effort to characterize the uptake and turnover of domoic acid by organisms in the food web. In addition to the commercially important species mentioned above, this effort should include finfish, other mollusks (including carnivores and snails), and krill. Uptake and turnover of domoic acid should be investigated both by species and by organ within each type of animal. It is anticipated that these efforts will be largely laboratory studies, but that they will be supplemented with field data collected during blooms of domoic acid-producing phytoplankton. The main purpose of these studies is to identify indicator or "sentinel" species in which the time frame of both uptake and retention are in appropriate balance.

Other desirable characteristics for indicator species are

- cosmopolitan distribution
- relative abundance
- ease of collection
- primary filter feeder (presumably)
- ease of domoic acid analysis

Mussels and barnacles were suggested as possibilities, assuming that uptake and retention studies gave promising results. (Of course, available evidence suggests that mussels of the Pacific Northwest may not take up or may turn over domoic acid too rapidly). Probably no single species will prove entirely satisfactory.

Direct Monitoring of Domoic Acid in Water

Research to develop simple, rapid, cheap methods for domoic acid detection would be very useful. This is primarily a biochemical problem. Having such a capability could prove of great value to biologists as well as to those monitoring for public health reasons.

Plankton Monitoring

Researchers in Canada have been highly successful in monitoring plankton. They have provided an early warning of impending toxicity in mussels by monitoring the development of blooms of domoic acid–producing phytoplankton species. In only a few years, Canadians have collected an impressive data base that is already proving of great practical value. Work should begin along comparable lines here.

This approach obviously depends on confirmation of the domoic acid–producing species and a vastly improved ability to survey, identify, and quantify phytoplankton off our shores. Relevant research topics are indicated above, in the Phytoplankton Working Group, and are not repeated here. The applicability of the Canadian model of course rests on an improved understanding of the ecological dynamics of the species and of domoic acid production in both locales.

Specific research goals are to standardize plankton collection methods and to improve identification methods, particularly of toxic or potentially toxic species (for example, immunological techniques and molecular probes).

Biomedical Research

There is a major need for extensive research on the toxicology of domoic acid and the medical risk factors associated with illness, including both chronic and acute effects. Comprehensive evaluation of research needs in this area lies outside the sphere of marine biology, but two topics did arise during the workshop that should be conveyed to biomedical researchers investigating the domoic acid problem.

First, long-term or chronic health risks associated with multiple exposure to low levels of domoic acid are unknown. Consideration of this aspect is especially important for risk evaluation. Present permissible levels of domoic acid in shellfish are based on our knowledge of the acute response to relatively high levels of domoic acid. If domoic acid toxicity can also result from the cumulative effects of multiple exposures, then current standards may be inadequate to protect public health.

Second, the neurotoxic effects of domoic acid poisoning occur in the brain. This indication that the toxin can cross the blood-brain barrier leads to the reasonable conclusion that it may cross other blood-tissue barriers. If so, then fetuses and pregnant women may be particularly vulnerable to domoic acid poisoning. An effort should be made to determine whether or not domoic acid can pass the placental barrier and, if so, what effect it has.

Epidemiology

Epidemiological studies may not be appropriate for Sea Grant, and, in any event, there are not many prospects for useful studies at this point. The relative risk of illness associated with exposure to available products is almost certainly so low as to demand impossibly large sample sizes for detection. Surveillance is difficult because of the impossibility of confirming the diagnosis under virtually any realistic conditions.

Report of the Shellfish Working Group

Chris Langdon (Oregon State University) and Neil Richmond (Oregon Department of Fish and Wildlife)

Judging from the experience of the Canadians, it is likely that domoic acid outbreaks will recur in subsequent years. It is clearly necessary to begin studies that will ultimately reduce health risks to shellfish consumers and reduce the adverse economic effects on recreational and commercial shellfisheries. The shellfish workshop consisted of representatives from the crab and oyster industries, state agencies (the Oregon Department of Fisheries and Wildlife and the Oregon Health Division), federal agencies (the Food and Drug Administration and the National Marine Fisheries Service), and academia. Four research areas that should be addressed to achieve these objectives were identified and prioritized.

1) The first priority is to establish a comprehensive shellfish-monitoring program on the west coast of the United States and Canada. The aim of this program would be to determine which species of shellfish are susceptible to domoic acid accumulation, with emphasis placed on edible species such as razor clams (deep and shallow water species), oysters, mussels, clams, Dungeness crab, sea urchins, and some fish species such as anchovy. From this information, indicator

species would be identified that could act as early-warning sentinels of domoic acid in the coastal environment. This information would be useful to state and federal health agencies who determine human health risks from the consumption of shellfish.

In addition, it is anticipated that the shellfish- and phytoplankton-monitoring programs be closely integrated, so that correlations can be made between oceanographic conditions, phytoplankton, and shellfish in regard to the spatial and temporal distribution of domoic acid in the coastal environment. Such an integrated program may lead to a comprehensive monitoring system that would provide shellfish harvesters, growers, and regulators with early warnings of potential domoic acid events. This type of program has been very effective in eastern Canadian waters in providing shellfish growers with almost two weeks of warning of domoic acid events, allowing growers to take precautionary measures, such as switching their harvesting to domoic acid–free estuaries.

2) Development of seafood processing methods that reduce concentrations of domoic acid in seafood would allow processors to minimize the health risks associated with the consumption of seafood contaminated by domoic acid. Research and testing should identify simple, economical procedures, such as depuration and frequent change of water used to boil crab meat.

3) We need to understand the mechanisms that determine the accumulation and fate of domoic acid in shellfish and fish. Such basic research would include studies of the feeding behaviors, uptake mechanisms, and rates of domoic acid accumulation from both particulate (phytoplankton, prey species, etc.) and dissolved phases. (In fact, the possibility of direct uptake of domoic acid from seawater has not, to our knowledge, been tested.) Investigations should include subsequent biochemical transformations in the tissues of shellfish and excretion of derivatives of domoic acid. Mechanisms and rates of loss of domoic acid from different species of shellfish wouldbe of interest to biologists and would also form a basis for depuration procedures of domoic acid–contaminated shellfish that could be adopted by industry.

It is also noteworthy that razor clams incorporate the domoic acid into body tissues (for example, foot and mantle), whereas mussels accumulate the toxin in digestive glands and rapidly depurate when placed in toxin-free water. Similarly, living Dungeness crabs probably accumulate the toxin only in the viscera, although toxin can enter crab meat during cooking if the crabs are not eviscerated before cooking. Depuration rates for razor clams and crabs are not known.

4) Domoic acid is highly toxic to mammals and is used as an insecticide and vermifuge in Japan. However, there have been no reports of adverse effects of domoic acid on the biology of shellfish, other marine invertebrates, or fish. Basic neurophysiological studies are required to understand why marine invertebrates, and possibly fish, appear immune to the effects of domoic acid. It is known that domoic acid mimics some neurotransmitter, most likely a glutamate type. Because it is water soluble, depuration is usually fast. However, the foot muscle of razor clams does not appear to depurate, and there does not appear to be a toxic effect. Some crustaceans are known to have glutamate receptors, yet crabs and other crustaceans do not appear to be affected. The answers to puzzles such as these are necessary if we are to identify indicator species. They are also likely to provide some basic comparative information on the mechanisms of neurotransmission.

5) Long-term, chronic health risks associated with consumption of low levels of domoic acid are also unknown. This aspect is especially important for setting the permitted level of domoic acid in tissue. If the toxicity is accumulative, then one could not help but worry about the levels currently being approved on the basis of acute responses in comparison to chronic dosages.

Such studies may lead to an increased understanding of the functioning of the nervous systems of animals and may result in the development of medical uses of domoic acid that would benefit human health or well-being.

Summary and Conclusions

The activities of utmost priority identified during the ASP Workshop are

1. to identify the source of domoic acid
2. to elucidate the factors governing domoic acid production
3. to establish a phytoplankton field study examining the processes that determine abundance and distributions of species
4. to establish routine toxicity monitoring in appropriate indicator species

Knowledge of the source of domoic acid, combined with information concerning its production, both spatially and temporally, may lead to a predictive capability for ASP outbreaks. While the predictions of outbreaks may be only one to two weeks in advance, this is sufficient time to modify harvesting procedures and protect the public, as shown by the Canadian example. The history of nuisance blooms along this coast and in most other regions of the world suggests that ASP will be a recurrent problem. By understanding the problem now, we may be able to save time, money, and lives in the future.

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APPENDIX 2: DOMOIC ACID AND *PSEUDONITZSCHIA* REFERENCES

This bibliography was compiled by Steve Bates, of the Department of Fisheries and Oceans, New Brunswick, Canada. If you are aware of any new literature or additional older material that is relevant, please contact Dr. Bates at the following address so that he can maintain this list.

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