

**TECHNICAL SEMINAR ON SAXITOXIN****1. Introduction**

- 1.1 From 23 to 24 September 1998, the Technical Secretariat convened a technical seminar on the different legitimate uses of saxitoxin. Eight of the ten internationally recognised scientists from six States Parties who attended the meeting at the invitation of the Technical Secretariat presented papers on the uses of saxitoxin for purposes not prohibited by the Convention. They also addressed the present and possible future impact on their work of the application of the transfer provisions under Part VI of the Verification Annex. In addition, 37 governmental experts and scientists from 22 States Parties also participated in the seminar. They came from National Authorities, public and private research laboratories, and industry, as well as from governmental institutions (ministries of health, trade and industry, and foreign affairs). A number of delegations present in The Hague sent observers to the seminar. The members of the Scientific Advisory Board attended part of the proceedings.
- 1.2 The intention of the seminar was to bring forward all pertinent technical information on present and projected future legitimate needs for access to saxitoxin, as well as on the impact of the Convention's transfer regulations on such use, with a view to assisting the Executive Council to resolve the issue of saxitoxin transfers. The seminar did not intend to discuss specific proposals to resolve the issue of saxitoxin transfers and also did not address the legal requirements for such a solution. It was understood that the issue of saxitoxin transfers remained on the agenda of the Executive Council.
- 1.3 The following is a concise factual summary of the proceedings of the technical seminar on saxitoxin. A statement prepared and signed by a group of participating scientists is attached (annex 1 to this report). Annex 2 to this report contains a list of the papers presented during the seminar, copies of which papers may be obtained from the Technical Secretariat upon request. The Technical Secretariat intends to publish the full proceedings of the seminar at a later stage.

2. Executive summary

- 2.1 Paralytic shellfish poisoning (PSP) is a global public health problem of increasing significance. In particular, there is a rapidly increasing need to monitor shellfish for PSP toxins. There is also a need to address the safety of drinking water in certain areas where PSP contamination has become a problem. At present, the red tide incidents which lead to PSP contamination cannot be predicted with any degree of certainty, as is also the case with the degree and duration of PSP contamination of shellfish. Consequently, both extended monitoring - in terms of the number of monitored locations and of the frequency of monitoring - and the ability to respond rapidly to red tide blooms are of critical importance to prevent the loss of human life.
- 2.2 There is at present no alternative to the use of saxitoxin as the calibration standard for such monitoring. PSP is today detected by the mouse bioassay, which requires saxitoxin for calibration purposes. The development of alternative techniques for PSP monitoring (e.g. high performance liquid chromatography (HPLC)) may lessen the need for saxitoxin transfers in the future. However, the validation of a new method prior to its international acceptance for regulatory testing, as well its introduction for regulatory testing, can take up to several years, and would also require transfers of saxitoxin. Only after the validation of such a new technique would the need for saxitoxin transfers for calibration purposes be reduced, but not altogether eliminated.
- 2.3 The quantities of saxitoxin required to monitor shellfish for PSP toxins are very small, and do not pose a risk to the object and purpose of the Convention. These quantities are far below a single lethal dose for humans.
- 2.4 With the implementation of the transfer provisions of the Convention in relation to Schedule 1 chemicals, the re-supply times for the calibration standards needed in regulatory PSP monitoring programmes have increased to a level which puts human lives at risk, and also impair the distribution and use of PSP test kits. Together with the impact of the transfer regulations on supplies of saxitoxin standards in general, these delays in re-supply times will severely hamper quality control in the fisheries industries, and will accordingly have a considerable economic impact on the commercial production and export of shellfish. Finally, legitimate research which is important for better understanding and counteracting PSP is being hampered. A workable solution which will enable timely re-supplies with saxitoxin calibration standards is urgently needed.
- 2.5 Moreover, certain tests for PSP monitoring that are currently being examined as alternatives to the mouse bioassay, as well as certain research projects which are important for the understanding and possible control and treatment of PSP incidents, and also for other biomedical reasons, depend on access to tritiated saxitoxin, supplies of which have effectively ceased. This problem also needs to be urgently addressed with a view to finding a solution as soon as possible.
- 2.6 The scientists present at the seminar urged the Organisation to take the action necessary to resolve these issues now. The seminar did not elaborate on the nature of the action to be taken, as the States Parties and the Executive Council are responsible

for dealing with this within the legal framework provided by the Convention. There was, however, consensus among the scientists that any further deferral of a decision on these issues would pose severe dangers to public health.

3. Monitoring paralytic shellfish poisoning - the humanitarian dimension

- 3.1 Seafood toxins are a pressing food safety issue. To deal with them, monitoring programmes have been (or need to be) established wherever people harvest or consume seafood. Paralytic shellfish poisoning is one of the most notorious seafood contaminations, and has been responsible for many deaths.
- 3.2 Saxitoxin is one of 18 different toxins involved in paralytic shellfish poisoning. It is a highly toxic metabolite produced by several marine dinoflagellates, and causes what is known as “red tides”. The toxin is accumulated in the tissue of shellfish filtering water for phytoplankton. Shellfish so contaminated retains the toxin for certain periods of time and, if consumed in this condition, is deadly to humans.
- 3.3 Furthermore, a bacterium has recently been linked to the contamination of drinking water supplies with saxitoxin.
- 3.4 It is at present impossible to predict with any degree of accuracy either the precise timing and location of red tide blooms or the duration of the contamination of shellfish with saxitoxin during and after such episodes. There are also at present no effective strategies to destroy or control red tide blooms. Thus, without effective food safety monitoring programmes, there is a high risk that humans may consume unsafe shellfish and die from PSP. No specific antidote to saxitoxin is presently available, with the result that a significant proportion of PSP intoxications result in death. Saxitoxin is rapidly emerging as one of the global public health problems of the twenty-first century.
- 3.5 In order to prevent the loss of human lives, more than 30 countries worldwide have introduced PSP monitoring programmes. This number is on the increase as a result of international efforts to improve consumer safety, and because shellfish imports are increasingly conditional on testing for PSP with an internationally accepted assay. An increase in PSP monitoring (by more countries, in more places, and with a higher frequency) has been internationally recommended for reasons of public health, as well as for economic reasons. This also applies to countries with no past record of red tide outbreaks.
- 3.6 At present, regulatory PSP testing is done by the mouse bioassay. This test, which has been accepted by the Association of Official Analytical Chemists (AOAC), is at this moment the only internationally accepted assay to certify the safety of shellfish for human consumption. Other tests that are being used are either outside the context of regulatory monitoring, or are under development or validation.
- 3.7 In order to address the increasing need for PSP monitoring, the utilisation of the mouse bioassay as the only regulatory test method will have to be reviewed, inter alia in relation to the availability of the capacity to breed sufficient numbers of test

animals. There is also an international trend to replace assays utilising test animals with alternative tests. Such alternative tests include high performance liquid chromatography, as well as other assays. In addition to providing alternatives to the mouse bioassay used today in regulatory monitoring, such new assays may also allow field testing by shellfish manufacturers. These new assays must be accurate, economic, quick, easily portable, and easy to perform. They would enable an increase in the frequency of PSP testing, and would thus improve the shellfish toxicity monitoring programmes, with the attendant reduction in risk to human life.

- 3.8 The mouse bioassay currently in use requires re-supplies with saxitoxin for calibration purposes. Typically, these standards are transported upon demand in very small quantities (for example, one supplier transports the standard in units containing 360 micrograms of saxitoxin dihydrochloride each in a 3.6 ml solution made of 20 percent aqueous ethanol). The development and validation of alternative tests, as well as their use - once validated and internationally approved - will also require access to saxitoxin as a reference compound and for calibration purposes (although physico-chemical methods such as HPLC, as opposed to assays based on biological principles, could use alternative calibration standards, their development and validation would depend on the availability of saxitoxin reference standards. At present, the HPLC standards applied for PSP testing do in fact contain small amounts of saxitoxin as a reference compound). The receptor binding assay, an assay that facilitates the simultaneous evaluation of large numbers of samples within a short period of time, also requires access to tritiated saxitoxin.
- 3.9 To sum up, there is at present no alternative to the use of saxitoxin as a calibration standard in PSP monitoring. Even with the introduction of new test techniques, transfers of saxitoxin would still be required, although possibly to a lesser degree. At the same time, the need for the routine testing of shellfish for PSP contamination is on the increase, in accordance with the increasingly global nature of the PSP problem. Given the unpredictable nature of the red tide phenomenon, delays in the supply of calibration standards will result in an unacceptable risk to human life. This problem needs to be resolved as a matter of urgency.

4. Monitoring paralytic shellfish poisoning - the economic dimension

- 4.1 In addition to the humanitarian dimension, monitoring for PSP toxins in shellfish has an economic dimension. Shellfish harvesting is an export industry in many States Parties which border on the sea. The seafood exports of such States Parties depend to a critical extent on the certification of the safety of such exports. Regulatory testing is thus not only an issue of food safety in the shellfish-consuming countries, but is also of central importance to the capacity of those States Parties which produce shellfish to export and sell what they have harvested.
- 4.2 The availability of test kits that could be used outside a laboratory by a layperson, or the introduction of other cheap, quick, simple and reliable tests that would enable the screening of large numbers of samples from a variety of locations, would make it possible for the seafood industry to further develop its own quality control regime. Manufacturers could thus schedule the harvest of their shellfish in such a way that

their products would be guaranteed safe for human consumption, and would satisfy the regulatory requirements for the marketing or export of these products. Such a quality control regime would have a significant economic impact on the seafood manufacturing industry, as it would eliminate the danger that entire harvests might have to be destroyed as unsafe.

- 4.3 There would appear to be no basis for economic concerns in relation to supplies with purified saxitoxin as a calibration standard or a reference compound. These standards are available from the US Food and Drug Administration (US FDA) as well as from the Canadian National Research Council (NRC), in one case on a non-commercial basis, in the other on the basis of cost recovery only. Consignments are sent directly to individuals if the suppliers are confident that the material will be used properly, and will not be made available for resale purposes. It also appears as though the commercial distribution of tritiated saxitoxin is based, not predominantly on economic incentives at the supplier's end, but on the needs of the community of users. There are, however, economic interests at stake for companies that - in response to existing health and safety concerns - develop and market PSP test kits for a broader community of users outside the realm of regulatory monitoring.

5. Saxitoxin in research

- 5.1 Saxitoxin is a highly selective sodium channel blocker and, as such, is an important research tool in the field of pharmacological and neurophysiological studies. Its availability affects a variety of fields of fundamental and applied biomedical research. Furthermore, many of these research applications require tritiated saxitoxin.
- 5.2 At the same time, access to saxitoxin is essential for research which is related to the occurrence, detection, and possibly treatment of PSP. The scientific understanding of the factors that trigger the occurrence of red tides remains very limited, and past models are frequently of very limited relevance. Thus, the prediction of red tides is fraught with uncertainty, as are predictions about the PSP contamination of shellfish during and after red tide events. Research into these environmental phenomena is crucial from a public health perspective, as it may eventually lead to both preventive strategies and effective control measures.
- 5.3 At the same time, the development and validation of new analytical procedures is essential to facilitate the necessary enhancement of the frequency and coverage of routine PSP monitoring (see subparagraphs 3.7 and 3.8 above). This, too, is essential public health research.
- 5.4 The research which is also being undertaken in the field of antidote development also depends on access to tritiated saxitoxin. Should such research lead to the development of an effective antidote for saxitoxin intoxication, the prevention of such intoxication through monitoring programmes could be combined with its specific treatment, resulting in the saving of additional lives.

- 5.5 To sum up, many research projects currently underway which depend on regular supplies of saxitoxin, and in some cases also of tritiated saxitoxin, are critically important from a public health perspective.

6. Impact of CWC regulations on re-supplies with saxitoxin

- 6.1 The application of the notification requirements for Schedule 1 transfers has considerably slowed down the re-supply of the saxitoxin standards required for calibration purposes. While such supplies could be delivered within days in the past, delivery can now be delayed by up to six or eight weeks. Given the unpredictability of both the occurrence of red tide incidents and the timing and duration of shellfish contamination with PSP toxins, such long delivery times carry the risk that re-supplies with saxitoxin calibration standards cannot be realised in a timely manner. If this issue is not resolved, it will continue to pose a serious and urgent problem to PSP monitoring, and will be accompanied by a significant risk of death from intoxication with contaminated shellfish.
- 6.2 In relation to those research and PSP monitoring activities that depend on the use of tritiated saxitoxin, the situation is that supplies have ceased for all but those States Parties which themselves have the capacity to purify saxitoxin to the required standard. Certain research programmes, including some into PSP antidotes, have consequently come to a complete halt.

Annex 1

STATEMENT BY PARTICIPATING SCIENTISTS

“We, the undersigned, as scientific experts participating in this meeting, agree that:

1. The 30 day notification period puts at risk human lives.
2. There is an urgent need for tritiated Saxitoxin for medical research and testing purposes.
3. That urgent research and health related needs could be accommodated by transfers of Saxitoxin in amounts of less than 5 mg.”

Signatures:

Joanne F. Jellett, Canada

Denise LeBlanc, Canada

S.G. Hudson, United Kingdom of Great Britain and Northern Ireland

Lyndon Llewellyn, Australia

Rhoda Azanza, Philippines

Laszló Maté, Hungary

Paulo Vale, Portugal

Elia Moreno, Mexico

Jorge Diogene, IOC/UNESCO

Ana Maria Amaro, Chile

Aija Jaunzeme, Latvia

Matrouk Hababba, Jordan

Mazen M. Khalil, Jordan

Annex 2**LIST OF PAPERS PRESENTED DURING THE SEMINAR**

1. Opening statement - John Makhubalo
2. Overview - Graham Cooper
3. Saxitoxins, an overview on current issues in research and management - Jorge Diogene
4. Interpretation of mouse bioassays for PSP aided by liquid chromatography (HPLC) and its implications for monitoring uses of saxitoxin - Paulo Vale
5. The uses of saxitoxin standards in the Philippines red tide monitoring and research activities - Zenaida Abuso and Rhodora Azanza
6. Diagnostic test kits for the aquaculture industry - Jellett Biotek
7. Real life strategies for red tide management in Chile: systematic application of receptor-based radioassays for PSP toxins in international seafood safety programmes - Benjamin Suarez-Isla et al
8. The novel saxitoxin binding protein, saxiphilin: its physiological role and applications - Lyndon Llewellyn
9. International distribution of reference standard saxitoxin and related material by the US Food and Drug Administration - Sherwood Hall
10. Saxitoxin and the Chemical Weapons Convention - Ron Sutherland

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