codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 2b) **CX/FFP 05/27/2-Add.1**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME
CODEX COMMITTEE ON FISH AND FISHERY PRODUCTS

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MATTERS REFERRED FROM FAO AND WHO: JOINT FAO/IOC/WHO AD HOC EXPERT CONSULTATION ON BIOTOXINS IN MOLLUSCAN BIVALVES

Short Summary of the Joint FAO/IOC/WHO *ad hoc* Expert Consultation on Biotoxins in Bivalve Molluscs

The Expert Consultation met in Oslo, Norway, Sept. 26-30, 2004 to provide scientific responses to the following specific questions posed by the CCFFP:

- Provide scientific advice to the CCFFP to enable the establishment of maximum levels in shellfish for shellfish toxins;
- Provide guidance on methods of analysis for each toxin group;
- Provide guidance on monitoring of biotoxin-forming phytoplankton and bivalve molluscs (including sampling methodology);
- Provide information on geographical distribution of biotoxin-forming marine phytoplankton.

Establishment of Guidance Levels/ Maximum Levels:

The Expert Consultation categorized the biotoxins into 8 distinct groups based on chemical structure. Then risk assessments were carried out in a stepwise fashion, including hazard identification, hazard characterization, exposure assessment and risk characterization. Based on the available information, the Expert Consultation derived the following provisional acute reference doses for four toxin groups: azaspiracid (0.04 µg/kg bw), okadaic acid (0.33 µg/kg bw), saxitoxin (0.7 µg/kg bw), and domoic acid (100 µg/kg bw). A provisional acute reference dose of 50 µg/kg bw was suggested for the yessotoxin group. The database for the cyclic imines, brevetoxins and pectenotoxins was insufficient to establish provisional acute reference doses for these toxin groups. Table 1 shows the derived guidance levels comparing results based on the consumption of 100g, 250g or 380g shellfish meat by adults.

It must be pointed out that the Expert Consultation did not have enough time to fully evaluate epidemiological data or to assess the effects of cooking or processing for deriving the provisional guidance levels/maximum levels for several toxin groups (especially the AZA and STX groups). The Consultation agreed that there is a need for a further in-depth review of these data to better derive the guidance levels/maximum levels.

Methods of Analysis

Test methods for the 8 toxin groups were reviewed and recommendations for Codex purposes have been made. Most methods currently available do not strictly meet criteria for Codex Type II or III methods. However, the recommendations represent the best currently available methods. The Expert Consultation recommended that where toxin groups are complex, the implementation of a marker compound concept and the use of functional assays should be explored. There is an urgent need to develop additional certified analytical standards and reference materials.

Specific Toxin Groups

AZASPIRACID (AZA) GROUP

- Limited data in humans indicate a lowest observable adverse effect level between 23 and 86 µg/person for acute gastrointestinal effects. The Expert Consultation established a provisional acute reference dose of 0.04 µg/kg bw. Because of insufficient data on the chronic effects of AZA, no tolerable daily intake could be established.
- No analytical methods currently meet Codex criteria for Type II or III methods. It is recommended that a liquid chromatography-mass spectrometry method be validated to fully meet Codex Type II or III criteria. Applicability of the technique is currently limited by the lack of certified analytical standards.

BREVETOXIN GROUP

- Only one episode of acute human illness has been reported for brevetoxins (estimated concentrations were 120-472 µg PbTx-3 equivalents/100g shellfish. The Expert Consultation agreed that there was insufficient data to complete the risk assessment. Chronic toxicity associated with brevetoxin ingestion is not known.
- No analytical method currently meets the criteria for a Codex Type II or III method. A liquid chromatography-mass spectrometry method or a functional assay should be validated to meet Type II or III criteria.

CYCLIC IMINES GROUP

- There have been no reports of adverse effects (acute or chronic) in humans.
- The Expert Consultation considered there was insufficient information to establish an acute reference dose or a tolerable daily intake for the cyclic imines.
- No analytical method currently meets the criteria for a Codex reference method. An existing liquid chromatography-mass spectrometry multi-toxin method should be validated to meet Type II or III criteria.

Domoic Acid (DA) group

- There was one well-documented episode of human toxicity involving 107 adults.
- Based on available data, a provisional acute reference dose of 0.1 mg DA/kg bw was established by the Expert Consultation.
- A liquid chromatography-UV detection method is recommended for consideration by Codex as the reference method.

OKADAIC ACID (OA) GROUP

- In humans, DSP causes acute gastrointestinal effects. The Expert Consultation established a provisional acute reference dose of 0.33 µg OA equ/kg bw, based on human toxicity data from several countries. No tolerable daily intake could be established because of insufficient data on chronic effects.
- No method exists that meets Codex criteria for a reference method. The most widely used analytical method is the mouse bioassay. However, it is prone to interferences from other toxins. The Expert Consultation recommends a liquid chromatography-mass spectrometry method be validated to fully meet Codex Type II or III criteria.

PECTENOTOXINS (PTX) GROUP

- There is no evidence of adverse acute or chronic health effects of pectenotoxins in humans. The Expert Consultation considered that the toxicity database was insufficient to establish an acute reference dose or a tolerable daily intake for these toxins.
- No analytical method exists that meets Codex criteria for a reference method. The Expert Consultation recommends that a liquid chromatography-mass spectrometry method be validated to fully meet Codex Type II or III criteria.

SAXITOXIN (STX) GROUP

- Human poisonings (including deaths) due to STX have been recorded for many years in many areas of the world. Based on the available data, the Expert Consultation established a provisional acute reference dose of 0.7 µg STX equivalents/kg bw. Because of insufficient data on the chronic effects of STX, no tolerable daily intake could be established.
- The AOAC mouse bioassay is widely used and has provided health protection in many member states for 60 years or more. The Expert Consultation noted several problems with the method that question its validity and use. A liquid chromatography-fluorescence method that has undergone an interlaboratory validation study appears to meet Codex criteria. It is recommended that this method be considered by Codex as a possible reference method.

Yessotoxin (YTX) group

- There have been no reports of ill effects in humans attributable to YTX. Based on animal data, the Expert Consultation established a provisional acute reference dose of 50 µg/kg bw. Because of insufficient data on the chronic effects of YTX, no tolerable daily intake could be established.
- No analytical method exists that meets Codex criteria for a reference method. The Expert Consultation recommends that a liquid chromatography-mass spectrometry method be validated to fully meet Codex Type II or III criteria.

Monitoring of Growing Areas

- The Expert Consultation agreed that decisions made on the safety of shellfish can only be based on the direct measurement of toxins in shellfish flesh. However, an integrated shellfish and micro-algal monitoring programme is highly recommended to provide expanded management capability and enhanced consumer protection. For early warning purposes it is recommended to have a programme to monitor growing areas for species of toxin-producing micro-algae. The programme should also include the evaluation of environmental conditions that may indicate the onset of harmful events.
- A micro-algal and shellfish sampling protocol over time and space should include the adequate location and number of sampling sites. Sample size and sampling frequency must be adequate to address spatial-temporal changes in micro-algae and toxins in shellfish.

Geographic Distribution of Phytoplankton

- Micro-algae responsible for the production of the toxins in the saxitoxin, domoic acid and okadaic acid groups, have a world wide distribution. Micro-algae responsible for the production of the remaining toxins have a more restricted geographical distribution. It is suggested that the distribution of all micro-algal species responsible for producing toxins be regarded as potentially worldwide.

Management of "new toxins" and "new" analogues

- In the case of human intoxication with an unknown "new" toxin, the Expert Consultation recommends that every effort should be made to identify the symptoms and clinical changes in affected individuals, in order to give information on the target site of the new toxin. Samples of the material associated with the intoxication should be gathered and stored for toxicology testing.
- For toxins for which adequate structure-activity data are available, a regulatory decision can be made on the basis of structure. If no adequate information is available, it is proposed that new analogues present in shellfish at less than 5% of the parent toxin should not be regulated against. Compounds present at a concentration greater than 5% of the parent compound should be isolated, characterized and then toxicological properties investigated in order to establish an acute reference dose or tolerable daily intake.

Recommendations:

To Member States, FAO, WHO:

- Encourage Member states to implement public health programs that ensure that shellfish poisonings are captured in a more systematic way.
- Encourage Member states to generate more toxicological data to perform more accurate risk assessments.
- Promote an increased international effort for the production of certified reference materials and calibration standards.
- Encourage Member states to improve and validate toxin detection methods in shellfish.
- Promote toxicological studies conducted according to OECD guidelines.
- Encourage studies to clarify the mechanism of action for a number of toxin groups.
- Encourage Member states to implement an integrated shellfish and micro-algae monitoring program.
- Consider the position of developing countries regarding implementation of chemical analytical methods.
- Encourage Member states to determine the relationship between quantitative occurrence of toxin producing micro-algae (planktonic and epiphytic) and the accumulation of biotoxins in bivalve molluscs.
- Encourage Member states to develop operational models for forecasting blooms of toxin producing micro-algae in time and space.

To Codex:

- Codex should continue to work on risk management recommendations (e.g. Standards and Code of Practice) to address issues related to biotoxins in bivalve molluscs.
- Consideration should be given to the situation in developing countries, when selecting detection methods.

To FAO, WHO:

- Establish a standing expert panel to periodically review scientific data and information at the international level. This panel should be convened soon to review epidemiological and cooking/processing data to more accurately derive guidance levels/maximum levels for some toxin groups.

Table 1: Summary data used in the derivation of acute reference doses, as well as derived and current guidance levels.

Toxin Group	LOAEL(1) NOAEL(2) µg/kg bw	Safety Factor (Human data (H) Animal data (A))	Provisional Acute RfD[a]	Derived Guidance Level/ Max Level based on consumption of 100g (1), 250g (2) and 380g (3)	Guidance Level/Max Level currently implemented in some countries[b]
AZA	0.4 (1)	10(H)	0.04 µg/kg 2.4 µg/adult	**0.024** mg/kg Shellfish Meat(1) **0.0096** mg/kg SM (2) **0.0063** mg/kg SM (3)	**0.16** mg/kg
BTX			N/A		0.8 mg/kg as PbTx-2
Cyclic Imines			N/A		
DA	1,000 (1)	10(H)	100 µg/kg 6mg/adult[a]	60 mg/kg SM(1) 24 mg/kg SM(2) 16 mg/kg SM(3)	20 mg/kg
OA	1 (1)	3(H)	0.33µg/kg 20 µg/adult[a]	0.2 mg/kg SM (1) 0.08 mg/kg SM (2) 0.05 mg/kg SM(3)	0.16 mg/kg
PTX			N/A		
STX	2 (1)	3(H)	0.7 µg/kg 42 µg/adult[a]	**0.42** mg/kg SM(1) **0.17** mg/kg SM(2) **0.11** mg/kg SM(3)	**0.8** mg/kg
YTX	5,000 (2)	100(A)	50 µg/kg 3 mg/adult[a]	30 mg/kg SM(1) 12 mg/kg SM(2) 8 mg/kg SM(3)	1 mg/kg

[a.] LOAEL= lowest observable adverse effect level; NOAEL= no observable adverse effect level.
[b] based on an adult bw of 60 kg