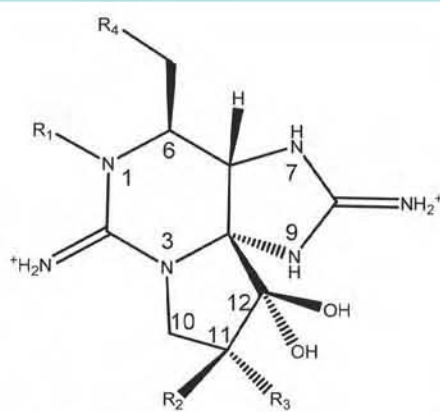
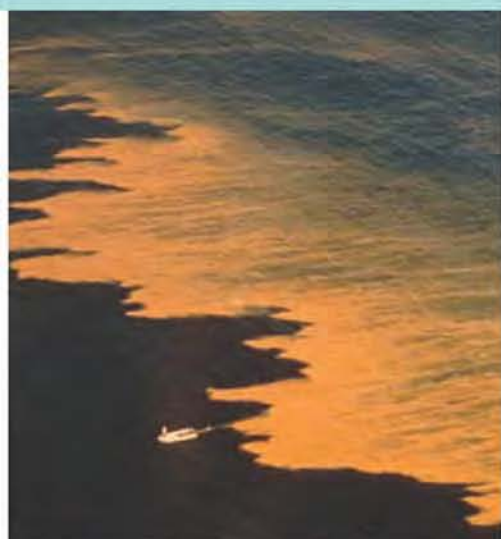
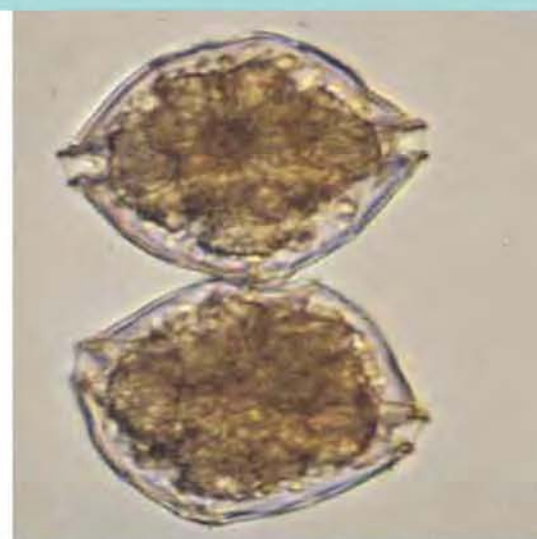


Assessment and management of biotoxin risks in bivalve molluscs



R ₁	R ₂	R ₃	R ₄	Toxin
H	H	H		STX
H	H	OSO ₃ ⁻		GTX2
H	OSO ₃ ⁻	H		GTX3
OH	H	H		NEO
OH	H	OSO ₃ ⁻		GTX1
OH	OSO ₃ ⁻	H		GTX4
H	H	H		GTX5 (B1)
H	H	OSO ₃ ⁻		C1
H	OSO ₃ ⁻	H		C2
OH	H	H		GTX6 (B2)
OH	H	OSO ₃ ⁻		C3
OH	OSO ₃ ⁻	H		C4
H	H	H		dcSTX
H	H	OSO ₃ ⁻		dcGTX2
H	OSO ₃ ⁻	H		dcGTX3
OH	H	H		dcNEO
OH	H	OSO ₃ ⁻		dcGTX1
OH	OSO ₃ ⁻	H		dcGTX4



Cover photographs:

Clockwise from top left: Picture of an algal bloom (red tide), courtesy of the Woods Hole Oceanographic Institution (WHOI), the United States of America; Chemical structure of saxitoxin and analogues (FAO); *Alexandrium tamarensis* cells, courtesy of WHOI; electron microscopic picture of *Alexandrium tamarensis* cell, courtesy of WHOI; Coffin Bay oysters, from Worldoutthere.net.

Assessment and management of biotoxin risks in bivalve molluscs

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Preparation of this document

At its 25th session held in Alesund, Norway, from 3 to 7 July 2002, the Codex Committee on Fish and Fishery Products (CCFFP) requested the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) to provide scientific advice on biotoxins in conjunction with its work for developing Standards for Live and Processed Bivalve Molluscs. The CCFFP, at its 26th session held in Alesund, Norway, from 13 to 17 October 2004, elaborated further the following specific questions to be covered through this advice:

- 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.

FAO, WHO and the Intergovernmental Oceanographic Commission of UNESCO (IOC) agreed to organize an Expert Consultation to address this request. First, a joint FAO/IOC/WHO workshop on biotoxins in bivalve molluscs was held in Dublin, Ireland, from 22 to 24 March 2004, to identify the scope, content of the work, candidates for the electronic drafting groups and information needed for compiling scientific advice to be discussed at the Expert Consultation.

In May 2004, three virtual working groups (WGs) were established to examine available data and information and to develop drafts for technical documents on: 1) analytical methods (Chair: Dr Philip Hess; Rapporteur: Dr Patrick Holland); 2) toxicological aspects (Chair: Dr Tore Aune; Rapporteur: Dr Tine Kuiper-Goodman); and 3) marine biotoxin management programmes (Chair: Mr Phil Busby; Rapporteur: Mr David Lyons).

The Expert Consultation met in Oslo, Norway, from 26 to 30 September 2004, to review the technical documents and prepare the report for the CCFFP. The Expert Consultation appointed Mr Phil Busby as Chairperson and Dr Jim Lawrence as Rapporteur. The experts were selected according to their scientific and technical expertise and to provide a balanced geographic distribution.

The draft report of the Oslo Expert Consultation was posted on the FAO Web site and presented at the 27th session of the CCFFP, held in Cape Town, South Africa, from 28 February to 4 March 2005. At that session, the CCFFP decided to establish a WG, chaired by Canada, that would work between the 27th and 28th sessions to examine the report from the Joint FAO/WHO/IOC Expert Consultation on Biotoxins in Bivalve Molluscs and prepare a discussion paper for consideration by the CCFFP with the following terms of reference:

- Assess how the CCFFP might use the expert advice and make recommendations with respect to approaches that the CCFFP could consider to integrate the advice into the Proposed Draft Standard for Live and Raw Bivalve Molluscs and the Section of the Code on Live and Raw Bivalve Molluscs.
- Identify new questions that the CCFFP may wish to pose to FAO/WHO.
- Identify areas in the report that may need further clarification.
- As appropriate, make recommendations on the validation of methodology (e.g. such as identifying other international organizations that are working in this area).

- As appropriate, make recommendations on possible changes to the Proposed Draft Standard for Live and Raw Molluscs and the Section of the Code on Live and Raw Bivalve Molluscs arising from the expert advice and other issues arising from the deliberations of the WG.

The WG – composed of Canada (Chair), Belgium, Chile, the European Community, France, Ireland, Japan, Mexico, the Netherlands, New Zealand, Norway, Spain, Thailand, the United Kingdom of Great Britain and Northern Ireland, the United States of America, Viet Nam and FAO – met in Ottawa, Canada, from 10 to 12 April 2006 to review a Discussion Paper prepared by Canada. This Discussion Paper provided an assessment of the Report of the Joint FAO/WHO/IOC Expert Consultation on Biotoxins in Bivalve Molluscs and made recommendations on standards and information to be included in the draft Codex Standard and Code of Practice on Bivalve Molluscs.

The WG report was examined by the CCFFP at its 28th session held in Beijing, China, from 18 to 22 October 2008. Most of the WG recommendations were used to finalize the biotoxins sections of the draft Code of Practice and Standard on Live and Raw Bivalve Molluscs. Both were advanced to Step 5 of the Codex procedure for adoption. They were further advanced to Step 8 at the 29th session of the CCFFP, held in Trondheim, Norway, from 18 to 23 February 2008, and were adopted by the 31st session of the Codex Alimentarius Commission (CAC) held in Geneva, Switzerland, during the period 30 June–4 July 2008, except for the Proposed Draft List of Methods for the Determination of Biotoxins in the Draft Standard for Raw and Live Bivalve Molluscs, which is being re-examined by an electronic WG led by Canada, with the view to developing performance criteria to assess the currently available analytical methods for biotoxins.

In order to satisfy the many requests received by FAO to disseminate the information collected over these years since 2004, the data and information available were edited and updated in 2009 and are presented hereafter in various chapters that compile scientific and technical information necessary for risk assessment, monitoring and surveillance programmes, and illustrate how CCFFP used international expertise to advance and finalize international standards for bivalve molluscs.

All papers have been reproduced as submitted.

Abstract

The present document compiles the scientific information collected by the experts for the Joint FAO/IOC/WHO ad hoc Expert Consultation on biotoxins in bivalve molluscs held in Oslo, Norway, 26–30 September 2004 to answer the request of scientific advice expressed by the Codex Committee for Fish and Fishery Products (CCFFP). In order to satisfy the many requests received by FAO to disseminate the information collected over these years since 2004, the data and information available were edited and updated in 2009. The document is organized in three main parts that present scientific and technical information necessary for risk assessment, monitoring and surveillance programmes and, in addition, illustrate how the CCFFP used international expertise to advance and finalize international standards for bivalve molluscs.

Part I is introductory and presents general information on the shellfish toxins selected for their involvement in poisoning events or their bioactivity observed in laboratory animals in combination with their repeated occurrence in shellfish, their physicochemical characteristics and their biogenetic, microalgal origins. It also provides data on bivalve mollusc production and trade and poisoning caused by bivalve molluscs. Consideration is given to the complex chemical nature of phycotoxins that results in many difficulties in obtaining sufficient quantities of all analogues and hampers the development and validation of methods for the evaluation of their toxicity and efficient control of limits. These difficulties and their impact on consumer protection and shellfish production are further discussed.

The interactions between risk evaluation and risk management as integral parts of risk analysis are outlined in the last section of Part I. While these general principles make the Codex approach very clear, it must be noted that specific risk analyses are far from trivial, in particular because of the frequent lack of data on toxin analogues, relative toxicities, exposure and epidemiology. This lack in data often makes risk assessments provisional and requires frequent review of the assessment and the management options derived.

Part II compiles the toxin group monographs prepared by the experts for the Expert Consultation and updated in 2009. The toxins were classified into eight groups based on chemical structure: the azaspiracid (AZA) group, brevetoxin (BTX) group, cyclic imines group, domoic acid (DA) group, okadaic Acid (OA) group, pectenotoxin (PTX) group, saxitoxin (STX) group, and yessotoxin (YTX) group. The reason for this was that for enforcement of Codex standards, chemical classification is more appropriate for analytical purposes than classification based on clinical symptoms. Each toxin monograph contains the following subsections:

- background information;
- origins and chemical data;
- biological data;
- analytical methods;
- levels and patterns of contamination of bivalve molluscs;
- dose response analysis and estimation of carcinogenic risk;
- evaluation;
- references.

Part II is completed by the summary of the FAO/IOC/WHO Expert Consultation. One of the conclusions of the Expert Consultation is 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 microalgal monitoring programme is highly recommended to provide expanded management capability and enhanced consumer protection.

The summary of the Expert Consultation also includes the replies to specific questions posed by the Codex Alimentarius and the recommendations to Member States, FAO, WHO and Codex. Three appendixes provide additional scientific information:

- Appendix 1 presents the concepts of marker compounds and relative response factors (RRFs). In this discussion paper, the definitions, practicality and limitations in use of marker compounds and RRFs are examined in the context of analysis for marine biotoxins in shellfish.
- Appendixes 2 and 3 present more detailed considerations about the marine biotoxin action plan and the role and design of phytoplankton monitoring in harmful algal bloom (HAB) programmes, from the documents collated by Working Group 3 of the Expert Consultation in 2004.

Part III illustrates how the Codex Alimentarius handled and used the expert recommendations for the management of the risk of biotoxins in bivalve molluscs. Three documents are provided:

- Report of the Working Group on assessing advice from the ad hoc expert consultation on biotoxins in bivalve molluscs;
- Codex Code of Practice for Processing Live and Raw Bivalve Molluscs;
- Codex Standard for Live and Raw Bivalve Molluscs.

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The rich and very informative report of that consultation was analysed and scrutinized by the members of the Working Group (WG) that met in Ottawa, Canada, from 10 to 12 April 2006. The WG, very ably chaired by Canada, provided vision and decisive guidance and options to the CCFFP on how to use the scientific and technical information to make management decisions in the form of a code of practice and a standard for bivalve molluscs.

The finalization of both the Code of Practice and Standard on bivalve molluscs benefited greatly from the many representatives of the countries that participated in the deliberations of the various sessions of the CCFFP and shared their national expertise and experience in managing the risk of biotoxins in seafood. This was made possible because of the effective and focused chairmanship of Mr Bjorn Knudtsen, chair of the CCFFP and the valuable and generous support of Ms Selma Doyran and Ms Verna Carolissen from the CCFFP Secretariat, and the scientific advice from FAO (L. Ababouch and H. Loreal) and WHO (H. Toyofuku).

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Abbreviations and acronyms

ADAM	9-anthryldiazomethane
AhR	aryl hydrocarbon receptor
ALT	alanine aminotransferase
AMPA/KA	amino-methyl proprionic acid/kainate
ANOVA	analysis of variance
AOAC	Association of Official Analytical Chemists
APEC	Asia Pacific Economic Cooperation
APHA	American Public Health Association
ARfd	acute reference dose
ASP	amnesic shellfish poisoning
AST	aspartate aminotransferase
AZA	azaspiracid
AZP	azaspiracid poisoning
BBB	blood brain barrier
BSA	bovine serum albumine
BTX	brevetoxin
b.w.	body weight
CAC	Codex Alimentarius Commission
CCFFP	Codex Committee on Fish and Fishery Products
CCMAS	Codex Committee for Methods of Analysis and Sampling
CE	capillary electrophoresis
CEN	Comité Européen de Normalisation (European Committee for Standardization)
CID	collision-induced dissociation
CK	creatine kinase
CNS	central nervous system
CoP	Code of Practice
CRL	European Community Reference Laboratory
CRM	certified reference material
DA	domoic acid
DG	digestive gland of shellfish; hepatopancreas
DMSO	dimethylsulphoxide
DNA	deoxyribonucleic acid
DRG	dorsal roots ganglia
DSP	diarrhoeic shellfish poisoning
DTX	dinophysistoxin
EAA	excitatory amino acid
EC	European Community

ECVAM	European Centre for the Validation of Alternative Methods
EEG	electroencephalogram
EFSA	European Food Safety Authority
ELISA	enzyme-linked immunosorbent assay
ESAC	ECVAM Scientific Advisory Committee
ESI	electrospray ionization
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FL	fluorescent method
GABA	gamma-aminobutyric acid
GEMS/Food	Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme
GFAP	glial fibrillary acidic protein
GI	gastrointestinal
GluRs	glutamate receptors
GYM	gymnodimine
G6PD	glucose 6-phosphate dehydrogenase
HAB	harmful algal bloom
HORRAT	Horwitz ratio (used to assess methods of analysis)
HP	hepatopancreas
HPLC	high-performance liquid chromatography
IAC	immunoaffinity column
IOC	International Oceanographic Commission of UNESCO
i.p.	intraperitoneal injection
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
i.v.	intravenous
JMPR	Joint Meeting on Pesticide Residues in Food and the Environment
KA	kainic acid
KB cells	a human cell line derived from epidermoid carcinoma
KT3	Killary Toxin-3
LC	liquid chromatography
LC-ESI/MSn	liquid chromatography-electrospray ionization mass spectrometry
LC-FL	liquid chromatography with fluorescence detection
LC-MS	liquid chromatography with mass spectrometry detection
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LC-UV	liquid chromatography with ultraviolet detection
LD50	median lethal dose
LDH	lactate dehydrogenase
LOAEL	lowest observable adverse effect level
LOD	limit of detection

LOQ	limit of quantitation
MAb	monoclonal antibody
MBA	mouse bioassay
MHX	mussel hepatopancreas extract
MLD	minimum lethal dose
MRM	magnetic resonance microscopy
MS	mass spectrometry
MSG	monosodium glutamate
MS/MS	tandem mass spectrometry
MTX	maitotoxin
MU	mouse unit
NMDA	N-methyl-D-aspartate
NOAEL	no observable adverse effect level
NRC	National Research Council of Canada
NSP	neurotoxic shellfish poisoning
OA	okadaic acid
OECD	Organisation for Economic Co-operation and Development
PbTx	polyether brevetoxin
PDE	phosphodiesterase
PET	positron emission tomography
PKC	protein kinase C
PLTX	palytoxin
PND	postnatal day
p.o.	per os, oral administration
PP1 and PP2A	protein phosphatase 1 and 2A
ppm	parts per million
PSP	paralytic shellfish poisoning
PTX	pectenotoxin
RBA	receptor binding assay
RfD	reference dose
RIA	radioimmunoassay
RNA	ribonucleic acid
RRF	relative response factor
RSDR	reproducibility relative standard deviation
RSDr	repeatability relative standard deviation
SANCO	Santé et Consommateurs (Directorate General of Health and Consumers, European Commission)
s.c.	subcutaneous
SIM	selected ion monitoring
SIR	selected ion recording
SPE	solid phase extraction
SPX	13-DM-spirolide

SRM	selected reaction monitoring
STX	saxitoxin
TDI	tolerable daily intake
TEER	transepithelial electrical resistance
TEF	toxicity equivalence factor
TLC	thin layer chromatography
TNF	tumour necrosis factor
TSH	thyroid-stimulating hormone, also known as thyrotropin
UV	ultraviolet
US FDA	Center for Food Safety and Applied Nutrition, Food and Drug
CFSAN	Administration of the United States of America
WF	whole flesh of shellfish
WG	working group
WHO	World Health Organization
WMX	whole mussel extract
YTX	yessotoxin