This is a paper for discussion. It does not reflect the views of the Committee and should not be cited.

TOX/2024/25

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

Advice on the risk to human health from consumption of bivalve molluscs (shellfish) harvested from UK waters associated with marine biotoxins

Introduction

1. The Food Standards Agency (FSA) is considering the current advice and monitoring programme for marine biotoxins and whether there is a need to update or change existing legislative standards.

2. The main purpose of this work is to identify any emerging marine biotoxins in UK waters, including considerations on increasing occurrence with increasing temperatures due to climate change. The views of the Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) were sought on whether any of these emerging marine biotoxins would pose a risk to human health.

3. A scoping paper on emerging biotoxins (TOX/2023/59) was presented to the COT at the December 2023 meeting. This paper provided an overview of potentially emerging biotoxins, brief summaries of any available toxicological information, occurrence data, with an emphasis on UK waters, and any additional relevant information, such as proposed or current limits/monitoring and considerations in other countries.

4. To assist the Committee in reaching a conclusion on which marine biotoxins potentially pose a risk to UK consumers, Members requested that the Secretariat

produce a) a table providing the main toxicological information of the marine biotoxins discussed in the scoping paper for easier comparison and b) a table of the main toxicological information of currently regulated marine biotoxins. This would help the Committee compare non-regulated biotoxins to those already monitored, and to enable Members to put the potential risk of emerging biotoxins into perspective.

5. The Committee requested that the table should include a summary of the toxicological endpoint(s), the lethal doses, and information regarding the occurrence of each biotoxin. Due to difficulties in fitting all required information into one single table, each biotoxin has been placed into an individual table summarising the requested information on occurrence, lethal doses, adverse effects, health-based guidance values (HBGVs), human intoxications, and any comments deemed relevant. Annex A provides information regarding the identified emerging biotoxins, Annex B provides information regarding regulated biotoxins.

6. All information regarding emerging biotoxins has been extracted from the original scoping paper (TOX/2023/59) and its references. All information regarding regulated biotoxins has been extracted from the appropriate EFSA scientific opinion.

7. In addition, a table (Annex C) has been included providing estimated adult exposures (78.6 kg bodyweight) to unregulated marine biotoxins, based on EFSA's shellfish portion size of 400 g, and a fish portion of 140 g, as suggested by the Ministry of Agriculture Fisheries and Food portion size book. Due to the limited nature of the occurrence data, the exposure assessment was done as an approximate estimate to aid Members in prioritisation rather than aiming to provide a full exposure assessment. The occurrence data used in the exposure assessment has previously been discussed in the scoping paper and summarised in Annex A. The original sources of the occurrence data for the respective biotoxins were a combination of surveillance studies, submissions by member states in response to EFSAs calls for data, country specific monitoring data, and research projects including laboratory-based studies and field studies.

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8. Please note, pinnatoxin (TOX/2023/37) and pectenotoxin (TOX/2023/58) have been discussed separately and have not been included in the tables.

Questions on which the views of the Committee are sought:

i. Does the Committee consider there to be enough information to conclude on which marine biotoxins potentially pose a risk to UK consumers, based on the toxicology and occurrence data?
ii. Based on the available information does the Committee consider it possible to comment on which marine biotoxins pose the highest risk to UK consumers (provide a risk ranking)?
iii. Are there any data gaps, or any further information the Committee would like to highlight?
iv. Does the Committee have any other comments.

Secretariat

July 2024

TOX/2024/25 – Annex A

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

Advice on the risk to human health from consumption of bivalve molluscs (shellfish) harvested from UK waters associated with marine biotoxins

The following table(s) summarise key occurrence data, and toxicological information, of the currently non-regulated marine biotoxins, as discussed in the scoping paper (TOX/2023/59).

Table 1: Brevetoxin (BTX), **Toxicological endpoint(s):** Neurotoxicity

Occurrence Data (Concentration/ Species/Country)	**HBGVs/Maximum levels permitted**	**Lethal dose (LD_{50}/LD_{100}/MLD) in animals**	**Human Intoxications**	**Adverse effect(s)/Symptoms**	**Comments**
82 to 345 µg/kg (BTX-2 + BTX-3; Mussels; France). 880 to 49,000 µg BTX-2 equivalents/kg (Shellfish; Mexico, New Zealand, USA). 580 to 6000 µg BTX-3 equivalents/kg	No regulatory limits in Europe. **USA** action level ≥ 0.8 mg BTX-2 equivalents/kg shellfish. **Australia/New Zealand**	**LD_{50}** Mice (i.p. administration; after 24 hours). • 170 - >300 µg/kg bw (BTX-3), • 200 – 400 µg/kg bw (BTX-(B)2) • 211 µg/kg bw (S-deoxy-BTX-B2), Mice (oral administration)	A few hundred intoxications reported but true number probably underestimated (ANSES,2021). No human fatalities or persistent symptoms reported (EFSA,	**Neurological/neurotoxic shellfish poisoning (NSP)** **Humans** Nausea, vomiting, diarrhoea, parasthesia, cramps, bronchoconstriction, paralysis, seizure, and coma. Recreational Irritant effect from inhalation/dermal exposure. **Animals**	Dermal exposure or inhalation can result in irritant effects. Inhalation occurs predominantly through breathing in aerosol from wave action. *MU: the amount of raw extract that kills 50% of mice within

(Fish; Mexico, New Zealand, USA).	Maximum level 20 MUs*/100g, BTX analogue not specified. **ANSES** proposed guidance level 180 µg BTX-3 equivalent/kg shellfish meat.	• 6600 mg/kg (BTX-2) • 520 mg/kg bw (BTX-3). Mice (i.v. administration) • 94 µg/kg bw (BTX-3) • 200 µg/kg bw (BTX-2). **MLD** Mice (i.p. administration) • 100 µg/kg bw (BTX-4; 6-24 hours) • 300 – 500 µg/kg bw (BTX-5; time of death not reported).	2010; CEFAS, 2014).	Depolarization of neuronal and muscle cell membranes resulting in impairment of the central and peripheral nervous system, including neurovegetative effects, neuromuscular effects, cardiorespiratory symptoms and central signs such as ataxia, seizure and decreased body temperature. ***In vitro*** Chromosomal aberrations (BTX-2) DNA damage (BTX-2/3/6/9) Evidence of DNA adduct formation (BTX-2).	930 minutes/15.5 hours.

Table 2: Cyclic imines (CIs) (Excluding PnTX and portimine), **Toxicological endpoint(s):** Neurotoxicity (SPX and GYM)

Occurrence Data (Concentration/ Species/Country)	HBGVs/Maximum levels permitted	Lethal dose (LD_{50}/LD_{100}/MLD) in animals	Human Intoxications	Adverse effect(s)/Symptoms	Comments
SPX: Norway, Spain, Italy. **Toxin producing organism**: Scotland, Italy,	**CRLBM/EURL** proposed guidance level 400 µg sum of SPXs/kg shellfish meat.	**LD_{50}:** Mice (i.p. administration) • 40 µg/kg bw (SPX mixture; crude extract),	No intoxications reported.	**Animals** Prostration and respiratory distress (mice recovered). Rapid systemic neurotoxicity and death. Inhibition of the muscarinic and nicotinic acetylcholine receptors (mAChR, nAChR) in the central and peripheral nervous system	EFSA calculated a margin of exposure (MOE) between the lowest oral LD_{50} values for SPX (50 and 500 µg/kg bw) in mice and the estimated 95th percentile of

Denmark, Ireland. PtTX and GYM not detected in Europe. GYM found in imported shellfish.		• 8 µg/kg bw (SPX C; fed mice), • 6.9 µg/kg bw (13-desmethyl SPX C; fed and fasted mice), • 27.9 µg/kg bw (13-desmethyl SPX C), • 8 µg/kg bw (20-methyl SPX G; fed mice), • 32.2 µg/kg bw (13,19-didesmethyl SPX C), • 450 µg/kg bw (GYM A; crude extract), • 96 µg/kg bw (GYM A; >95% pure), • 80 µg/kg bw (GYM A),		and the neuromuscular junction (SPX and GYM).	exposure (0.06 µg/kg bw) from consumption of shellfish currently on the market. The MOE ranged from 1000-10000. EFSA concluded that the estimated exposure to SPXs did not raise concern for the health of the consumer. (The LD_{50s} can be found in Table 8, for SPX-C).

		• 800 µg/kg bw (GYM-B), • Overall, 500-1005 µg/kg bw (SPX). Mice (oral administration) • 1000 µg/kg bw (SPX; crude extract), • 176 and 780 µg/kg bw (SPX C; fed), • 53 and 500 µg/kg bw (SPX C; fasted), • 157 and 1005 µg/kg bw (13-desmethyl SPX C; fed), • 125, 500, 591 and 625 µg/kg bw (13-desmethyl SPX C; fasted),			

		• 157 and 625µg/kg bw (20-methyl SPX G; fed), • 88 and 500 µg/kg bw (20-methyl SPX G; fasted), • 755 and 4057 µg/kg bw (GYM A; >95% pure). Mice (i.c. administration) • 3 µg/kg bw (GYM-A). **LD_{100}** Mice (i.p. administration) • 250 µg/kg bw (SPX B,D). **LD_0** Mice (oral administration) • 625 µg/kg bw (SPX C; fed),			

		• 400 µg/kg bw (SPX C; fasted), • 780 µg/kg bw (13-desmethyl SPX C; fed), • 400 µg/kg bw (13-desmethyl SPX C; fasted), • 500 µg/kg bw (20-methyl SPX G; fed), • 400 µg/kg bw (20-methyl SPX G; fasted). **MLD** Mice (i.p. administration) • 700µg/kg bw (GYM A; crude extract).			

Table 3: Palytoxin (PITX), **Toxicological endpoint(s):**

Occurrence Data (Concentration/ Species/Country)	**HBGVs/Maximum levels permitted**	**Lethal dose (LD_{50}/LD_{100}/MLD) in animals**	**Human Intoxications**	**Adverse effect(s)/Symptoms**	**Comments**
300 to 625 µg/kg shellfish meat	No regulatory limits set.	**LD_{50}** (i.p. administration)	Intoxications reported.	**Humans**	

(PITXs; Mussels and sea urchins; France; Greece; Italy; Spain;).	**EFSA** ARfD for sum of PITX and ostreocin-D: 0.2 µg/kg bw. **NRL for Marine Biotoxins** provisional limit 250 µg/kg shellfish. **ANSES** Short term toxicity reference value for PITX 0.08 µg/kg bw per day.	• Rabbit: 0.025 µg/kg bw, • Dog: 0.33 µg/kg bw, • Monkey: 0.078 µg/kg bw, • Mouse: 0.45 µg/kg bw, • Rats: 0.089 µg/kg bw, • Guinea pigs 0.11 µg/kg bw, Mice (oral administration) • 510-767 µg/kg bw, Rat (oral administration) • 40 µg/kg bw (> 24 hours).	Some reports of severe cases including fatalities from consumption of contaminated shellfish. (Deeds and Schwartz 2009 in EFSA,2009), Poisoning cases reported where exposure occurred through injured skin and inhalation. For some cases reported involvement of PITX not confirmed (CEFAS,2014).	Myalgia and weakness, possibly accompanied by fever, nausea and vomiting, and rhabdomyolysis, characterised by injury to skeletal muscle, muscle breakdown and leakage of myocytes into plasma. Renal failure and disseminated intravascular coagulation. Death. Skin, eye and respiratory irritation. **Animals** Reduced intracellular pH. Rabbits increased metabolism of arachidonic acid and the production of eicosanoids; arachidonic acid metabolised to prostaglandins, releasing norepinephrine and contracting the aorta. Mice Scratching, stretching of hind limbs, significant weight loss, lower back and concave curvature of the spinal column, muscle spasms, respiratory distress, dyspoea and progressive muscular paralysis. Histopathological changes in the heart, kidney, liver, pancreas, intestines and lymphoid tissues. Reduced lymphocytes in tissues (0.25 µg/kg bw PITX five times a week up to 29 times). Increased plasma concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) (≥ 36 µg/kg bw). Changes to blood sodium and chloride levels. Increased blood potassium levels.	

				Tumour promotion (two-stage mouse skin carcinogenesis model) ***In Vitro*** Cytotoxic (EC_{50}s of 5 x 10^{-10} M and 2 x 10^{-7} M for rat and cattle erythrocytes, respectively) PITX and ovatoxins-a (OVTX) affect the integrity of the intestinal barrier (at concentrations of 0.5 and 5 ng/mL in Caco-2 cells). Increased IL-8 (PITX, OVTX-a AND OVTX-d).	

Table 4: Saxitoxin (STX), Toxicological **endpoint(s):** Neurotoxicity

Occurrence Data (Concentration/ Species/Country)	**HBGVs/Maximum levels permitted**	**Lethal dose (LD_{50}/LD_{100}/MLD) in animals**	**Human Intoxications**	**Adverse effect(s)/Symptoms**	**Comments**
Toxin producing algae: Norway, Portugal, France, Germany, Italy, Turkey, Egypt.	**EU** 800 µg STX equivalents/kg shellfish meat. **FAO/IOC/WHO** provisional ARfD of 0.7 µg STX equivalents/kg bw. **EFSA** ARfD 0.5 µg STX equivalents/kg bw. **ANSES**	**LD_{50}** Mice (i.p. administration) • 10 µg/kg bw. Mice (oral administration) • 260-263 µg/kg bw.	Intoxications reported, including fatalities from respiratory arrest. Children have a higher mortality rate.	Paralytic shellfish poisoning (PSP). **Humans** Mild symptoms: slight tingling sensation, numbness, mostly around the lips but spreading to face and neck, headache, dizziness, nausea. Moderately severe symptoms: incoherent speech, progression of prickling sensation to arms and legs, stiffness, non-coordination of limbs, general weakness and feeling of lightness, slight respiratory difficulties and rapid pulse.	EFSA proposed TEFs based on acute toxicity in mice. The TEFs range from 0.1-1; for all TEFs please see paragraph 83 of TOX/2023/59.

	TRV ~ 0.1 µg/kg bw. **OHA** TDI 0.05 µg/kg bw per day. **Interim drinking water guidance levels** 1 µg/L (Australia, New Zealand and OHA) 3 µg/L (Brazil, Australia, and WHO). **Recreational guidance values** 75 µg/L (Washington State) 10 µg/L (OHA). **OEHHA** Interim notification level 0.6 µg/L.			Severe to extremely severe symptoms: muscular paralysis, pronounced respiratory difficulties to fetal respiratory paralysis. Death from respiratory arrest. **Recreational** Skin and eye irritation. **Animals** Cat, Rabbit. Decreased respiratory activity, weakening of muscle contractions, decreased action potential amplitude and longer latency time in peripheral nervous system (1-2 µg STX/kg bw). Respiratory depression and death (4-5 µg STX/kg bw). Hypertension (> 1 µg STX/kg bw). Neurotoxicity, changes in total antioxidant capacity, production of reactive oxygen species in the brain and liver, decrease in glutamate cysteine ligase, aversive memory performance, increase in GST and amino acid neurotransmitters, acute alterations of dopamine. Rats Reduction in bodyweight and feed intake (6 µg/kg neoSTX) Zebra fish: sublethal reversible morphological and sensory motor effects. Fish Reduced growth and survival during larval development. ***In Vitro***	

				DNA damage in fish neuronal cells (3 µg/L STX equivalent). **Mechanism of toxicity** Binding to voltage-gated sodium channels, clocking conductance, acting on nerve and muscle fibres.	

Table 5: Tetrodotoxin (TTX), **Toxicological endpoint(s):** Neurotoxicity

Occurrence Data (Concentration/ Species/Country)	**HBGVs/Maximum levels permitted**	**Lethal dose (LD_{50}/LD_{100}/MLD) in animals**	**Human Intoxications**	**Adverse effect(s)/Symptoms**	**Comments**
TTX and analogues: 0.0003 to 0.541 mg/kg (gastropods and bivalves; France; Spain; Italy; Greece; The Netherlands; Ireland; UK). TTX most common analogue in all regions.	No maximum levels in the EU. **EFSA** ARfD 0.25 µg/kg bw. **Kasteel et al. (2017)** ARfD 1.33 µg/kg bw. **Finch et al. (2018)** ARfD 10.1 nmol/kg (3.2 µg/kg). **Unknown** 110 µg TTX equivalent/kg shellfish meat (Reference not found, taken from a review by Katikou 2019 citing the	**LD_{50}** Mice (i.p. administration and s.c. administration) • 8-13 µg/kg bw Mice (oral administration and intragastric administration) • 232 µg/kg bw and 532 µg/kg bw **LD_{100}** Mice (oral administration) • 1000 µg/kg bw **MLD** • 2 mg (40 µg/kg bw, 50 kg	Some human case reports. Onset of symptoms within 10-45 minutes of ingestion, although delayed responses of 3-6 hours have also been reported. (EFSA, 2017; Lago et al, 2015).	**Humans** Perioral numbness and paraesthesia, with or without GI symptoms to lingual numbness, early motor paralysis, incoordination, slurred speech with normal reflexes, to generalised flaccid paralysis, aphonia and fixed/dilated pupils to hypoxia, hypotension, bradycardia, cardiac dysrhythmias and unconsciousness. Death, caused by respiratory failure and cardiac collapse. **Animals** Skeletal muscle fasciculation, apathy, lethargy, ataxia, ascending progressive paralysis and death. Mice: urine production significantly decreased (at 75 µg/kg and 125 µg/kg daily). Exposure at the highest concentration resulted in changes to the kidney and myocardium. ***In Vitro***	TTX and STX are additive. ARfD for TTX could alternatively be set at the same level as that for STX, equating to 0.43 µg/kg for TTX (Finch et al. 2018). No antidote for TTX. MLD: EFSA were unable to retrieve the underlying data/original source.

	study Kasteel et al. 2017).	Japanese adult).		Inhibited neuronal electric activity (in rat primary cortical cultures and human-induced pluripotent stem cell-derived iCell neurons). Spindle fibre aberration in the human lymphocyte chromosome aberration test (following exposure of with crude extracts from skin/liver of the porcupine fish containing TTX at 0.5 mg/mL).	

Table 6: Novel azaspiracids (AZAs), **Toxicological endpoint(s):**

Occurrence Data (Concentration/ Species/Country)	**HBGVs/Maximum levels permitted**	**Lethal dose (LD_{50}/LD_{100}/MLD) in animals**	**Human Intoxications**	**Adverse effect(s)/Symptoms**	**Comments**
Japan	No information available.	No information available.	None reported	No information available.	None.

Table 7: Novel PSP analogues domoic acid analogues, **Toxicological endpoint(s):**

Occurrence Data (Concentration/ Species/Country)	**HBGVs/Maximum levels permitted**	**Lethal dose (LD_{50}/LD_{100}/MLD) in animals**	**Human Intoxications**	**Adverse effect(s)/Symptoms**	**Comments**
No information available.	No information available.	No information available.	None reported.	No information available.	None.

Table 8: Cyanobacteria toxin(s), **Toxicological endpoint(s):** Depending on cyanotoxin, ranging from neurotoxicity, hepatotoxicity, cytotoxicity to dermal toxicity and irritation.

Occurrence Data (Concentration/ Species/Country)	**HBGVs/Maximum levels permitted**	**Lethal dose (LD_{50}/LD_{100}/MLD) in animals**	**Human Intoxications**	**Adverse effect(s)/Symptoms**	**Comments**

Northern Ireland (Lough Neagh). **MCs:** <100 µg/kg fresh weight (Fish muscle; Europe). 45 to 142 µg MC-LR/kg fresh weight (Saltwater mussels; Greece). **NOD**: 80 to 817 µg/kg dw (Shellfish; Finland; Poland). **BMMA:** 900 to 14,000µg/kg (Oysters; France; Sweden; Greece). **2 DAB:** 1,100 to 9,700 µg/kg (Mussels; France). **DAB:** 1,300 to 8,800 µg/kg(Oysters; France) **AEG:**	**MCs:** **EFSA** TDI of 0.04 µg/kg bw per day. **ANSES** Subchronic TRV 1 ng/kg bw per day. **WHO** Provisional TDI of 0.04 µg/kg bw. **OHA** TDI of 0.05 µg/kg (for MC-LR specifically). **ATX:** **WHO** No formal TDI set. NOAEL 98 µg/kg bw per day. **CYN:** **WHO** TDI of 0.03 µg/kg bw. **ANSES** subchronic TRV of 0.14 µg/kg bw per day **OHA** applied EPAs oral RfD 0.03 µg/kg per day **ATX-a:**	**LD_{50}** Mice (i.p. administration) • 32.5-158 µg/kg bw (MC-LR), • 111-650 µg/kg bw (MC-RR), • 110 and ~171 µg/kg bw (MC-YR), • 140 and 171 µg/kg bw (MC-WR), • 100 and ~249 µg/kg bw (MC-FR), • 249 µg/kg bw (MC-AR), • 39 µg/kg bw (MC-LA), • 91 µg/kg bw (MC-LY), • 50–70µg/kg bw (NOD), • 40-749 µg/kg bw (includes,	Fatalities due to MC exposure (WHO,2020)	**Humans** MCs Most commonly gastroenteritis Intrahepatic haemorrhage Fatalities (after mistreated water used in dialysis). BMAA Implicated in neurodegenerative diseases: Amyotropic lateral sclerosis, Parkinsonism-dementia complex, and Alzheimer's. **Animals** MCs Lung effects (thickening of the alveolar septum, disruption of cell junctions, alveolar collapse, and lung apoptosis). Serum profile changes (increase in transaminases, decrease in total proteins). Effects on the nervous system (cognitive impairment, lesions, oxidative injury, inflammation in brain regions). Reproductive and developmental effects (decreased sperm number and motility, abnormal sperm morphology, lesions in the testes, testicular atrophy, change in serum hormone concentrations, impact on the ovaries) (OEHHA, 2021). Tumour promotion in rodents: Possible carcinogen to humans (Group 2B).	For cyanotoxin studies there's a lack of available standards/purified toxins. Extracts were often used, which are poorly characterised. Available data on MCs indicated an up to 30-fold difference in acute toxicity, following i.p administration compared to the oral route. For further information and references for LD50 values see Table 3.3.1.1 Data on MC acute toxicity in mammals expressed as LD50 values (Testai et al., 2016).

1,400 to 1,700 µg/kg (Mussels and Oysters; France). **ATX/CYN**: detected in fish (Excl. Europe).	**OHA** TDI of 0.1 µg/kg per day.	-Anatoxin-a, ±Anatoxin-a, +Anatoxin-a, and Anatoxin-a) • 100-352 (24h) and 45.5-189 (7 d) μg_{equiv}/kg bw (CYN), • 116 µg crude extract/kg bw (CYN). 9 other MC variants range from ~90 to 750 µg/kg bw. Rat (i.p administration) • 72-122 µg/kgbw (MC-LR), • 5.3 µg/kg bw (±Anatoxin-a)		Inhibition of PP1 and PP2A leading to cytoskeleton alterations, lipid peroxidation, oxidative stress, apoptosis, resulting in hepatic centro-lobular toxicity with intrahepatic haemorrhagic areas due to damage of sinusoidal capillaries (MC-LR, > 32 µg/kg bw). ATX Rapid death. ATX-a Increased heart rate and blood pressure, fatigue, eventual muscle paralysis and potential death. BMAA Neurotoxic in rats and monkeys Long term histopathological changes in the brain of adult rodents Alterations of the intermediate metabolites, i.e. d-glucose, lactate, 3-hydroxybutyrate, acetate, creatine, in neonatal rats. NOD Reproductive toxicity: loss of spermatogenesis, apoptotic changes in spermatogonia (pyknotic and shrunken), atrophic change in the prostate epithelium with apoptosis (nuclear dusts). CYN Increased liver and kidney weight, hepatic and renal toxicity. Maternal toxicity including vaginal bleeding and blood in tail tips, hepatocytes. necrosis and kidney lesions, alterations of haematological parameters, and death. **In Vitro**	

		Mice (oral administration), • 5-10.9 mg/kg bw (MC-LR), • 16.2 mg/kg bw (+Anatoxin-a), • 4400-6900 (2-6 days) μg_{equiv}/kg bw (CYN). Rat (oral administration) • >5mg/kg bw (MC-LR). Mice (i.v. administration) • 28 µg/kg bw (MC-LR), • 630 µg/kg bw (GSH-MC-LR conjugate), • 267 µg/kg bw (Cys-MC-LR conjugate), • 91 µg/kg bw (MC-YR)		MCs Induction of oxidative stress and apoptosis in human cell lines (MC-LR). BMAA Neurotoxic in rodent and leech cells, and human cell lines. Disturbs undifferentiated cells (B1 and C cells) at 100 µM, promotes proliferation, affects the organisation of neuroblasts. Increased the release of proinflammatory cytokines (IL-1β, IL-6, TNFα) Promotes cell death, induces subcellular changes in neurons and Mueller Glial Cells (at concentrations of 0.4 µM (3 days) and 0.4,1 and 10 µM (3 and 9 days)). NOD Micronuclei containing centromeres in HepG2 cells (5 and 10 µg/mL for 24h) Increased basal DNA strand breaks in HepG2 cells (1-10 µg/mL up to 24h) Enhanced 8-oxo-dG, a common biomarker of oxidative DNA damage, in primary cultured hepatocytes (2 and 10 ng/mL).	

		• 304 µg/kg bw (GSH-MC-YR conjugate), • 217 µg/kg bw (Cys-MC-YR conjugate). Rat (i.v. administration) • 80 µg MC-LR equiv/kg bw (MC-LR and RR), • 400 µg/kg bw (±Anatoxin-a), • 85 µg/kg bw (+Anatoxin-a).			

TOX/2024/25 – Annex B

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

Advice on the risk to human health from consumption of bivalve molluscs (shellfish) harvested from UK waters associated with marine biotoxins

The following table(s) summarise key occurrence data, and toxicological information, of current regulated marine biotoxins extracted from the appropriate EFSA scientific opinion.

Table 9: Saxitoxin, **Toxicological endpoint(s):** Neurotoxicity

See Annex A: Emerging Biotoxins, Table 4, for further details.

Table 10: Domoic Acid, **Toxicological endpoint(s):** Neurotoxicity

Occurrence Data (Country/ Species/ Concentration)	**HBGVs /Maximum levels permitted**	**Lethal dose (LD_{50}/LD_{100}/ MLD) in animals**	**Human Intoxications**	**Adverse effect(s)/Symptoms**	**Comments**

UK, Ireland, France, Spain, Portugal, Denmark, Norway, Italy, Germany, Netherlands. Shellfish.	**EU** 20 mg DA/kg shellfish meat. **EFSA** ARfD 30 µg DA/kg bw. **FAO/IOC/WHO** Provisional ARfD 100 µg/kg bw 6 mg/adult (person with 60kg bw).	**LD_{50}** Mice (i.p. administration; female): • 5.8mg/kg bw (median lethal dose; mussel extracts), • 2.9-3.6mg/kg bw (mussel extracts), • 3.6-4.0 mg/kg bw (pure toxin).	**Canada** 107 cases (47 men and 60 women) met criteria for ASP from consuming mussels; 19 hospitalised, 4 died. 143 cases had suspected poisoning with DA, but this was not confirmed. Estimated exposure for clinical symptoms, 60-290 mg, (equivalent to 0.9-4.2 mg/kg bw). **USA** 11-24 cases of ASP from EU 160 µg AZA1 equivalents/kg shellfish meat consuming razor clams. 13 had mild neurological symptoms, 7 sought medical assistance. Highest concentration detected in clams was 140 µg/g tissue. For mild symptoms,	**Humans** Amnesic Shellfish Poisoning (ASP) including gastrointestinal symptoms (vomiting, diarrhoea, or abdominal cramps) and/or neurological symptoms (confusion, loss of memory, potential seizure, or coma). **Animals** Mice (oral administration) Scratching (35 mg/kg bw) *, clinical signs (not detailed; 71 mg DA/kg bw; acidified extract), death (71 to 83mg DA/kg bw; acidified extract). Rats (oral administration) Flaccidity, head on floor, inactivity, mastication, seizures, mild to moderate CNS damage, death (n=1-4; given 60-80 mg/kg bw DA *per os*). Monkey (oral administration) Mild to moderate histopathological lesions in CNS consistent with neuroexcitation (5 to 10 mg/kg bw). Anorexia, salivation, retching, vomiting, licking, and smacking of lips and empty mastication's (when given crude or purified DA; 5 to 10 mg/kg bw). Diarrhoea and prostration (in animals receiving mussel extracts; ~6 mg DA/kg bw). Mice (i.p. administration) Scratching of the shoulders by the hind leg (1mg/kg bw), convulsions (≥2.0mg/kg) and often death. Hypoactivity, sedation, akinesia, rigidity, stereotypy, loss of postural control and tremors. Rats (i.p. administration)	No data available on LD_{50} in male mice. Occurrence data provided as the sum of DA and epi-DA, distinction was possible between the concentration of parent DA and epi-DA. *No effects at doses of 20 and 28 mg/kg bw, death occurred at 47 and 104 mg/kg b.w. Several doses between the latter two levels were devoid of any effect, suggesting other factors were modifying the toxicity. In a very early study (1959), anthelminthic effects occurred in 3 children at oral doses of a DA-like compound at 0.4, 0.64 and 0.8mg/kg bw.

			concentrations ranged from 0.05-0.39 mg/kg bw. Reporting of this incident was queried and causality attributed to DA questioned.	Withdrawal followed by hyperexcitation and scapular scratching (2 mg/kg bw). Histopathological lesions in the hippocampus (CA3>CA1>CA4), hypothalamus, amygdala, cortex, olfactory system, and retina and showed wet dog shakes, rearing with forelimb extension - “praying”, loss of balance and seizures (≥4 mg/kg bw). Increased serum T3 and T4 levels (30 minutes after injection) and TSH levels (5 minutes after injection) (1mg DA/kg bw). Hypomotility and decreased body weight (0.93 mg DA/kg bw). Symptoms suggestive of hyperreactive syndrome, together with neuronal degeneration in the hippocampal CA1/CA3 areas and gliosis (1.32 mg DA/kg bw). Neuronal injury, astrocytosis, activation of microglia and alterations in fatty acid metabolism (2.25 mg DA/kg bw). Developmental toxicity: death of dams (2.0 mg/kg) and pre-term abortion (50 % of rats in the 1.75 mg/kg group). Induction of c-fos in the central nervous system (0.1 mg/kg bw in neonatal rats), behavioural effects and seizures (at doses as low as 0.05 and 0.2 mg/kg bw). Monkey (i.p. administration) Persistent chewing with frothing, gagging, emesis, loss of balance and tremors and excitotoxic central nervous system damage consisting of dendrotoxic and gliotoxic edema and nerve cell degeneration in structures of the limbic system and the retina (4 mg/kg bw DA).	

				Mice (i.v. administration) Developmental toxicity: impairment of hippocampal function and morphology, and delayed cell necrosis in offspring (0.6 mg DA/kg bw on gestational day 13). Rat (i.v. administration) Seizure discharges in the hippocampus, tonic-clonic convulsions, and death (0.5-1.0 mg/kg bw DA). Monkey (i.v. administration) Neuroexcitatory, emetic (0.025-0.2 mg/kg bw). Excitotoxic (0.5 mg/kg bw DA). Clinical signs of neurotoxicity. Nausea, damage to neurons and degeneration in the brain (0.25 to 4mg/kg). Mice (subcutaneous injection) Developmental toxicity: neurobehavioural sequelae in offspring (0.3, 0.6 and 1.2 mg/kg; to pregnant rats on GD13). Motor seizures characterized by scratching, tail flicking, and swimming-like movement (at all doses; 0.10, 0.17, 0.25, 0.33, 0.42, and 0.50 mg/kg). Paralysis (doses ≥ 0.33 mg/kg; in 65% of rats), and death (47%) in less than 2 hours. Changes in brain development in the absence of convulsions (neonatal rats injected daily; 5 and 20 µg/kg). ***In Vitro*** Increase in the frequency of micronuclei (in Caco-2 Cells)	

Table 11: Okadaic Acid (and OA group toxins), **Toxicological endpoint(s):** Gastrointestinal (DSP)

Occurrence Data (Country/ Species/ Concentration)	**HBGVs /Maximum levels permitted**	**Lethal dose (LD_{50}/LD_{100}/ MLD) in animals**	**Human Intoxications**	**Adverse effect(s)/Symptoms**	**Comments**
Denmark, France, Germany, Ireland, The Netherlands, Norway, Portugal, Spain, Sweden, UK. Shellfish. 48 to 6550 µg/kg shellfish.	**EU** 160 µg OA equivalents/kg shellfish meat. **FAO/IOC/WHO** ARfD 0.33µg OA equivalents/kg bw.	**LD_{50}** Mice (i.p. administration): • 204 µg/kg bw, • 200 µg/kg bw , • 225 µg/kg. **Lethal dose** Mice (i.p. administration): • 200 µg/ kg bw. Mice (oral administration): • 400 to 600 µg/kg bw, • Between 1,000 and 2,000 µg/kg bw.	DSP reported in Japan, the Netherlands, Norway, Sweden, Belgium, Portugal, UK, Canada, Chile and New Zealand. **Japan** 164 people suffering with diarrhoea, nausea, vomiting and abdominal pain from eating mussels or scallops containing mostly DTX1. Intakes estimated 48 µg OA equivalents/person for mild symptoms or 80-280 µg OA equivalents/person for severe symptoms.	**Humans** Diarrhoeic Shellfish Poisoning (DSP): diarrhoea, nausea, vomiting and abdominal pain. Fever, chill, and headache. **Animals** Mice Intestinal injury (200 µg/kg bw) and liver injury (375 µg/kg bw i.p. administration and 1000-2000 µg OA/kg bw). Hypersection in the small intestine (75, 150 and 250 µg/kg bw), severe mucosal injury, extravasion of serum into lamina propria of villi, degeneration of absorptive epithelium of iliac villi, and desquamation of the degenerated epithelium from the lamina propri. Erosion of the small intestine, stomach, and large intestine (150 µg/kg bw OA) and diarrhoea (90 µg/kg bw). Rats Intestinal injury (375 µg/kg bw) and liver injury (375 µg/kg bw). Swollen villi enterocytes with detachment from basal membrane.	OA group includes OA, DTX1 and DTX2, and DTX3. The analogues tested by member states varied, and in some cases only the sum for the combined OA group-toxins was reported, without information on specific analogues detected. (EFSA,2008), No information available on long term effects or repeated exposure in humans.

			Portugal 6 cases from consuming: razor clams: 500 µg OA equivalents /kg flesh. 1 case from consuming green crabs: 322 µg OA equivalents /kg edible crab parts. **Norway** 200 cases from consuming leftovers from crab meals, DTX3 levels at 1,050 to 1,500 µg OA equivalents/kg brown meat. 39 cases from consuming mussels at 550-650 µg OA equivalents/kg shellfish flesh. **UK** 159 cases from consuming mussels at 258-302 µg OA equivalents/kg shellfish flesh.		

Table 12: Dinophysis toxins, **Toxicological endpoint(s):** Gastrointestinal (DSP; as part of OA group)

Occurrence Data (Country/ Species/ Concentration)	**HBGVs /Maximum levels permitted**	**Lethal dose (LD_{50}/LD_{100}/ MLD) in animals**	**Human Intoxications**	**Adverse effect(s)/Symptoms**	**Comments**
Denmark, France, Germany, Ireland, The Netherlands, Norway, Portugal, Spain, Sweden, UK. Shellfish. Of 6072 samples: **DTX 1.** 416 samples ≥ LOD up to 160 µg toxin/kg shellfish meat. 89 samples >160 µg toxin /kg shellfish meat. **DTX2** 302 samples ≥LOD up to 160 µg	None specific for DTX. See Table 3 for HBGVs for OA equivalents.	**LD_{50}** Mice (i.p. administration): • 350 µg/kg bw (DTX2). **Lethal dose** Mice (i.p. administration): • 160 µg/kg bw for (DTX 1), • 200 to 500 µg/kg bw. (DTX 3). Mice (oral administration): • 300 µg/kg bw (DTX1).	See Table 3.	**Humans** As part of OA group toxins, See Table 3. **Animals** Mice (i.p. administration). Intestinal injury (50-500 µg/kg bw for DTX1 and at 375 µg/kg bw for DTX3) Bleeding in the abdomen (DTX3). Mice (oral administration). Light diarrhoea and slight reduced bodyweight. Light erosions to the stomach, intestinal damage (600 and 700 µg/kg). Mice and rats (i.p. administration). Liver injury (375µg/kg bw; DTX1 and DTX3). Mice and rats (oral administration). Liver injury (750 µg/kg bw DTX3).	

toxin/kg shellfish meat. 66 samples >160 µg toxin /kg shellfish meat. **DTX3** 1495 samples ≥ LOD up to 160 µg toxin/kg shellfish meat. 149 samples >160 µg toxin /kg shellfish meat.					

Table 13: Yessotoxins (and analogues), **Toxicological endpoint(s):**

Occurrence Data (Country/ Species/ Concentration)	**HBGVs /Maximum levels permitted**	**Lethal dose (LD_{50}/LD_{100}/ MLD) in animals**	**Human Intoxications**	**Adverse effect(s)/Symptoms**	**Comments**
Germany, Italy, Norway, Portugal, Spain, United Kingdom. Shellfish. “not detected” to 9620 µg YTX	**EU** 1 mg YTX eq./kg shellfish meat. **EFSA** ARfD 25 µg YTX equivalents/kg bw 3.75 mg YTX eq./kg shellfish meat.	**LD_{50}*** Mice (i.p. administration; male). • 80-462 µg/kg bw (YTX), • 301 µg/kg bw (Di-desulfoYTX),	No reports of human illness.	**Humans** No reports on adverse effects in humans. **Animals** Mice (i.p. administration). Dyspnoea and death (≥ 300 µg/kg). Restlessness and jumping before death at lethal doses. Shivering (at 750 and 1000 µg/kg) and cramps.	Analytical methods of identifying levels of toxin in shellfish varied including ELISA, HPLC, LC-MS/MS. *,** See Table 10, EFSA 2008 for further details regarding mouse

eq./kg shellfish meat.		Mice (i.p. administration; female), • 112-750 µg/kg bw (YTX), • 444 µg/kg bw (1a-HomoYTX). **Lethal dose **** Mice (i.p. administration; sex not reported) • 100 µg/kg bw (1a-HomoYTX), • ~500 µg/kg bw (45-HydroxyYTX; 55-Carboxy-1a-homoYTX 7; 55-CarboxyYTX), • ~220 µg/kg bw (45,46,47-TrinorYTX), • ~500 µg/kg bw (1-DesulfoYTX).		Vacuolation in the cardiac muscle, and intracellular oedema, cardiac damage (500 µg/kg), swelling of myocardial cells (5-10mg/kg) and alterations of myocardiocytes (1-2 mg/kg YTX). Cytoplasmic protrusions of myocardiocytes, rounding of mitochondria and fibre modifications (1mg/kg 1a-homoYTX and 45-hydroxyYTX). Altered disposal of E-cadherin. ***In Vitro**** Phosphodi-esterase activation, modulation of calcium movements at several levels, calcium dependent cAMP and cGMP decrease, altered protein disposal, apoptosis and cell death, and changes in cell shape (at 10^{-6} to 10^{-10}M YTX).	strain and references. No information available on LD_{50} of YTX-group toxins via the oral route. ***For detail regarding cell type, species, time frame, and references, see Table 9, EFSA 2008.

Table 14: Azaspiracids, **Toxicological endpoint(s):** Gastrointestinal (similar to DSP)

Occurrence Data (Country/ Species/ Concentration)	HBGVs/ Maximum levels permitted	Lethal dose (LD_{50}/LD_{100}/ MLD) in animals	Human Intoxications	Adverse effect(s)/Symptoms	Comments
Germany, Ireland, Norway, UK. Shellfish "not detected" to 1630 µg/kg shellfish meat.	**EU** 160 µg AZA1 equivalents/kg shellfish meat. **EFSA** ARfD 0.2 µg AZA1 equivalents/kg bw.	**Lethal dose** Mice (i.p. administration; male) • 200µg/kg bw (purified AZA1), • 110 µg/kg bw (AZA2), • 140 µg/kg bw (AZA3), • 470 µg/kg bw (AZA4), • 1000 µg/kg bw (AZA5). Indicative values only due to low number of animals used due to limited pure toxins.	AZA poisoning reported across the Netherlands, Ireland, Italy, France, and the UK. **Netherlands** 8 cases, unwell after consuming 8-10 mussels harvested from the west coast of Ireland. Intakes estimated initially between 6.7 µg (5th percentile) and 24.9 µg (95th percentile) per person, with a median of 14.5 µg per person (2001). Revised estimate in 2005/6 was between 50.1 µg (5th percentile) and 253.3 µg (95th percentile), with a median of 113.4 µg per person. **Italy**	**Humans** AZA poisoning (AZP): nausea, vomiting, diarrhoea and stomach cramps. **Animals** Mice (oral administration), Shortened villi, injury to small intestine (600 or 700 µg/kg bw; slow recovery after 24h). 38% increase in liver weight after 24h, fine fat droplets distributed in liver (500 µg/kg bw). Dose-dependent necrotic lymphocytes in the thymus, spleen, and Peyer´s patches of the small intestine (500 to 700 µg/kg bw), Changes to the small intestine: congestion, watery substance in the lumen, small changes to surface epithelial cells, atrophic lamina propria spatially separated from epithelial cells and prominent vacuolization of epithelial cells (300 µg/kg bw). Lethality (single oral doses; from 250 to 600 µg/kg). Decreased body weight, ballooning and gastrointestinal organs containing a lot of gas. Pathological changes: lung (interstitial inflammation and congestion, tumours), stomach (erosion), small intestine (shortened villi, oedema, and atrophic lamina propria) and liver (some cases - single or focal necrosis, small	Some longer term repeated-dose toxicity studies (maximum duration 1 year) showed occasional lung tumours. As these tumours were only observed at doses causing severe toxicity, they were considered of little relevance.

			10 cases. **France** 20-30 cases. **UK** 12-16 cases. Cases in Italy, France and UK related to consumption of mussels or scallops imported from Ireland. No estimates of AZAs consumed available.	inflammation, mitosis, or congestion) (50 and 20 µg/kg). ***In Vitro*** Increase of Ca 2+ (EC_{50} 10^{-6} to 10^{-7} M). Increase of cAMP (EC_{50} 10^{-6} to 10^{-7} M). Decrease in pH (EC_{50} 10^{-6} M). Cytotoxicity ((EC_{50} 10^{-6} to 10^{-9} M). Altered F-actin cytoskeleton (EC_{50} 10^{-5} and 10^{-8} M). Cell adhesion (EC_{50} 10^{-8} to 10^{-9} M).	

TOX/2024/25 – Annex C

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

Advice on the risk to human health from consumption of bivalve molluscs (shellfish) harvested from UK waters associated with marine biotoxins

Table 15: Estimated adult exposures (78.6 kg bodyweight) to unregulated marine biotoxins, based on EFSA's shellfish portion size of 400 g, and a fish portion size of 140 g, as suggested by the Ministry of Agriculture Fisheries and Food portion size book.

Toxin	Occurrence	HBGVs	Exposure Assessment in Adults
Brevetoxin.	82 to 345 µg/kg (BTX-2 + BTX-3; Mussels; France). 880 to 49,000 µg BTX-2 equivalents/kg (Shellfish; Mexico, New Zealand, USA). 580 to 6000 µg BTX-3 equivalents/kg (Fish; Mexico, New Zealand, USA).	No regulatory limits set. **EFSA** ARfD for sum of PITX and ostreocin-D: 0.2 µg/kg bw. **NRL for Marine Biotoxins** provisional limit 250 µg/kg shellfish. **ANSES** Short term toxicity reference value for PITX 0.08 µg/kg bw per day.	0.42 to 1.8 µg/kg bw. 4.5 to 250 µg/kg bw. 1.03 to 11 µg/kg bw.

Cyclic imines (excluding PnTX and portimine).	SPX: Norway, Spain, Italy. Toxin producing organism: Scotland, Italy, Denmark, Ireland. PtTX and GYM not detected in Europe. GYM found in imported shellfish.	**CRLBM/EURL** proposed guidance level 400 µg sum of SPXs/kg shellfish meat.	N/A
Palytoxin (PITX).	300 to 625 µg/kg shellfish meat (PITXs; Mussels and sea urchins; France; Greece; Italy; Spain;).	No regulatory limits set. **EFSA** ARfD for sum of PITX and ostreocin-D: 0.2 µg/kg bw. **NRL for Marine Biotoxins** provisional limit 250 µg/kg shellfish. **ANSES** Short term toxicity reference value for PITX 0.08 µg/kg bw per day.	1.5 to 3.2 µg/kg bw.
Saxitoxin (STX).	Toxin producing algae: Norway,	**EU**	N/A

	Portugal, France, Germany, Italy, Turkey, Egypt.	800 µg STX equivalents/kg shellfish meat. **FAO/IOC/WHO** provisional ARfD of 0.7 µg STX equivalents/kg bw. **EFSA** ARfD 0.5 µg STX equivalents/kg bw. **ANSES** TRV ~ 0.1 µg/kg bw. **OHA** TDI 0.05 µg/kg bw per day. **Interim drinking water guidance levels** 1 µg/L (Australia, New Zealand and OHA) 3 µg/L (Brazil, Australia, and WHO). **Recreational guidance values** 75 µg/L (Washington State) 10 µg/L (OHA). **OEHHA** Interim notification level 0.6 µg/L.	

Tetrodotoxin (TTX).	TTX and analogues: 0.0003 to 0.541 mg/kg (gastropods and bivalves; France; Spain; Italy; Greece; The Netherlands; Ireland; UK). TTX most common analogue in all regions.	No maximum levels in the EU. **EFSA** ARfD 0.25 µg/kg bw. **Kasteel et al. (2017)** ARfD 1.33 µg/kg bw. **Finch et al. (2018)** ARfD 10.1 nmol/kg (3.2 µg/kg). **Unknown** 110 µg TTX equivalent/kg shellfish meat. (Reference not found, taken from a review by Katikou 2019 citing the study Kasteel et al. 2017).	0.0015 to 2.8µg/kg bw
Novel azaspiracids (AZAs).	Japan	No information available.	N/A
Novel PSP analogues domoic acid analogues.	No information available.	No information available.	N/A
Cyanobacteria toxin(s).	Northern Ireland (Lough Neagh) **MCs:**	**MCs:** **EFSA** TDI of 0.04 µg/kg bw per day.	**MCs:** 0.18µg/kg bw.

	<100 µg/kg fresh weight (Fish muscle; Europe). 45 to 142 µg MC-LR/kg fresh weight (Saltwater mussels; Greece). **NOD**: 80 to 817 µg/kg dw (Shellfish; Finland; Poland). **BMMA:** 900 to 14,000µg/kg (Oysters; France; Sweden; Greece). **2 DAB:** 1,100 to 9,700 µg/kg (Mussels; France). **DAB:** 1,300 to 8,800 µg/kg(Oysters; France). **AEG:** 1,400 to 1,700 µg/kg (Mussels and Oysters; France). **ATX/CYN**: detected in fish (Excl. Europe).	**ANSES** Subchronic TRV 1 ng/kg bw per day. **WHO** Provisional TDI of 0.04 µg/kg bw. **OHA** TDI of 0.05 µg/kg (for MC-LR specifically). **ATX:** **WHO** No formal TDI set. NOAEL 98 µg/kg bw per day. **CYN:** **WHO** TDI of 0.03 µg/kg bw. **ANSES** subchronic TRV of 0.14 µg/kg bw per day. **OHA** applied EPAs oral RfD 0.03 µg/kg per day. **ATX-a:**	0.23 to 0.72µg/kg bw. **NOD:** 0.41 to 4.2µg/kg bw. **BMMA:** 4.6 to 71µg/kg bw. **2 DAB:** 5.6 to 49µg/kg bw. **DAB:** 6.6 to 45µg/kg bw. **AEG:** 7.1 to 8.7µg/kg bw. **ATX/CYN:** N/A.

		OHA TDI of 0.1 µg/kg per day.	

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