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TOXINS OCCURRING IN FISH, CRUSTACEA AND SHELLFISH – A REVIEW

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It is common knowledge that fish are a nutritious component of a human diet, as they constitute a valuable and desired source of protein and polyunsaturated fatty acids. Crustacea and shellfish, consumed chiefly for their high sensory values, also demonstrate a similar nutritive value as well as provide zinc that improves the functioning of the nervous system. Nevertheless, seafood are likely to pose risk to consumer's health since they contain a variety of toxins. In addition, the risk is magnified by the fact that those toxins are usually thermo-resistant and cannot be eliminated by such treatments as cooking.

INTRODUCTION

Fish belong to food products with a very high nutritive value which approximates that of meat, hence, fish are a perfect food, mainly due to the content of protein. Fish protein is readily available (at a level of 96%) due to a low content of collagen and elastin, *i.e.* from 5 to 10%. In comparison, in beef those values fluctuate between 8 and 20%, which affects meat tenderness. It is worth mentioning that as small as a 100-g ration of fish provides a human with $^1/_3$ to $^1/_2$ of the daily requirement for animal protein. Fish constitute an important and indispensable component of a human diet also due to the content of polyenoic fatty acids of the *n*-3 family. They are necessary for comprehensive development and functioning of brain as well as sight and auditory senses. They also lower blood cholesterol level and exhibit antiatherosclerotic activity [Sikorski, 2004].

In recent years, a growing interest has been observed in crustacea and shellfish. These products are highly valued for their sensory traits. Their nutritive value is similar to that of fish. Fish contain high amounts of calcium and phosphorus, and especially valuable iodine occurring in the saltwater species of fish. In contrast, seafood products (oysters, mussels, crabs and shrimps) are a rich source of zinc, which improves the functioning of the entire nervous system.

Although fish, crustacea and shellfish are a valuable source of food, their consumption may contribute to food poisoning and infections once they contain toxins. Most of these toxins are usually produced by species of naturally occurring marine algae and accumulate in fish and crustacea or shellfish, when they feed on the algae or on other fish that have fed on the algae [Backer *et al.*, 2005].

FISH TOXINS

Regulation concering toxins in fish

According to Regulation (EC) No.853/2004 of the European Parliament and of the Council of the 29 April 2004 (laying down specific hygienic rules for food of animal origin), fishery products originating from poisonous fish of the following families: Tetraodontidae, Molidae, Diodontidae and Canthigasteridae, cannot be introduced into the market. This applies also to fishery products containing biotoxins, *e.g.* ciguatoxin, and muscle palsy-inducing toxins.

Tetrodotoxin

The most lethal toxin that accumulates in fish is tetrodotoxin. It is lethal both for a human and other mammals, birds, most fish and other marine animals, yet some species of puffer fish and salamanders have developed tolerance to that toxin [Watters, 1995]. The concentration of tetrodotoxin varies depending on the body part of fish, with the highest values reported for liver and ovary, followed by intestines and skin [Mahmud *et al*., 2000].

Noguchi *et al*. [1986], Simidu *et al*. [1987] have advanced and proven the hypothesis that this toxin is produced by bacteria belonging to the genera: Bacillus, Micrococcus, Aeromonas, Moraxella or Flavobacterium. Animals, *e.g.* puffer fish, absorb and accumulate tetrodotoxin through the food chain. A contrary view was held by Matsumura [1998], who pointed to an endogenous origin of tetrodotoxin in the puffer fish. In the course of that study, ovulating oocytes were collected and then subjected to artificial insemination and cultured. The level of toxin in embryos was observed to increase

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continuously along with their growth, thus indicating that the elevating concentration of tetrodotoxin originates from the embryos, since it is unlikely that the embryos would be capable of absorbing the toxin from the medium. Yet, the mechanism of biosynthesis in the puffer fish is still under scrutiny.

The activity of tetrodotoxin consists in inhibiting the generation and conduction of neural impulses through blockage of sodium channels [Watters, 1995; Isbister & Kiernan, 2005]. Clinical symptoms evoked by toxin poisoning develop rapidly and their intensification depends mostly on the intake of toxin. The first symptoms are sensory in character, including a numb sensation in mouth region and lower limbs as well as disorders of sensation. In the case of benign poisoning, only sensory symptoms are observed to develop that are accompanied by weaker manifestations of gastrointestinal disorders, *i.e.* nausea and vomiting. Patients with moderately severe poisoning manifest the following symptoms: muscle weakness, vertigo, and then ataxia. Severe intoxication leads to aphonia, persistent mydriasis, generalized flaccid paralysis and respiratory insufficiency, however, patients remain conscious. Severe and life-threatening poisoning with tetrodotoxin is characterized by cardiovascular symptoms (bradycardia, hypotension and dysrhythmia), respiratory insufficiency and coma [Watters, 1995; Isbister & Kiernan, 2005]. In the case of severe and lethal intoxication, symptoms develop within 1 hour. Most fatal cases occur in the first 20–30 minutes. If the patient survives the first 24 h, they have good chances of recovery [Watters, 1995]. In the case of moderately severe poisoning, the symptoms appear after 90 minutes. In moderate poisoning, most of symptoms regress after 5 days, whereas cases of poisoning with a benign course may last for as little as a few hours [Isbister & Kiernan, 2005]. No antidote exists in the case of tetradotoxin poisoning, hence, palliative treatment is recommended, *e.g.* in the case of bradycardia use can be made of atropine. Occasionally, the use of a respirator is necessary in the first 24–72 h.

Ciguatoxin

Ciguatoxin is the most common toxin that accumulates in tropical fish [Pearn, 2001; Lewis, 2001]. Mortality induced by that toxin is extremely rare as it accounts for *ca*. 0.1% [Bagnis *et al*., 1979]. Dinoflagellates *Gambierdiscus toxicus* produce gambiertoxin which is subject to biotransformation into a more polar ciguatoxin. Coral reef fish feeding on dinoflagellates accumulate ciguatoxin which does not have any significant, letal impact on them. Yet, at the top of the food chain it may induce a severe intoxication in humans, referred to as "ciguatera". *Gambierdiscus toxicus* predominates in warmer months, which is reflected in the seasonality of poisonings. *Gambierdiscus toxicus* is also a source of other marine toxins referred to as maitotoxins. The latter are produced by all strains of *G. toxicus*, however, each strain produces only one type of this toxin. Maitotoxins are mainly detected in the intestines of herbivorous fish and do not play any role in the ciguatera fish poisoning syndrome. In contrast, ciguatoxin is produced only by selected strains of *G. toxicus* and accumulates in the liver, muscles, skin and bones of predatory fish [Lehane & Lewis, 2000, Chinain *et al*., 1999]. Ciguatoxin is stable and cannot be inactivated by such treatments as cooking, freezing, salting or pickling. Fish accumulating this toxin originating from tropical areas may be consumed in every season, irrespective of the site of their catch area [Watters, 1995]. While poisonous fish containing ciguatoxin retain normal taste, aroma or appearance, at higher concentrations of the toxin they are likely to demonstrate behavioral or morphological changes, and even induce a lethal effect [Lehane & Lewis, 2000].

The mechanisms of ciguatoxin action is linked with a direct effect on excitable nervous and muscular layers, mainly on their capacity for the generation and conductance of action potential. Ciguatoxin is characterized by the ability to bind with voltage sensitive sodium channels, leading to their opening in the membranes of resting cells. It is manifested by an inflow of Na^+ ions, cell depolarization and appearance of a spontaneous action potential in excited cells. The cardiovascular effect, evoked by ciguatoxin activity, results from the positively inotropic impact on myocardium. By acting on voltage sensitive Na^+ – channels ciguatoxin evokes an inflow of Na^+ ions to the cell's interior. This, in turn, activates mechanisms as a result of which the cell expels Na^+ ions and absorbs calcium. Although a considerable increase in calcium concentration is buffered by sarcoplasmic reticulum, a local increase in calcium concentrations leads to an increase in the force of myocardium contraction. A similar mechanism of inducing an intracellular inflow of calcium, induced by ciguatoxin, is observed in cells of intestinal endothelium. It contributes to the enhanced secretion and is manifested by diarrhea [Lehane & Lewis, 2000].

Ciguatoxin intoxication is characterized by gastrointestinal disorders (vomiting, diarrhea and contractions of abdominal cavity organs), neurological symptoms (headaches and nausea, ataxia, sensibility disorders, muscular and joint pains), itching of the skin of palm, feet and lips, as well as less common cardiovascular symptoms (arrhythmia, bradycardia or tachycardia, reduced blood pressure) [Watters, 1995; Isbister & Kiernan, 2005]. Changes are also likely to involve the central nervous system, leading to hallucinations and coma [Pearn, 2001; Arena *et al*., 2004; Perez *et al*., 2001]. Most ciguatoxin intoxication cases were observed after the consumption of fish containing the toxin at a concentration of 0.1–5.0 μg/kg.

Symptoms of ciguatoxin intoxication usually persist for 1–2 weeks, yet in some patients they may reappear in the 8th week after the initial symptoms. Generally, neurological symptoms last longer than the gastrointestinal disorders and in some cases they have been reported several years later [Swift, 1993].

There is no antidote in the case of ciguatoxin poisoning, only adjunct therapy is undertaken. Since ciguatoxin is very soluble in fats, its absorption from the intestine is rapid and considerable. Nevertheless, early occurrence of vomiting and diarrhea may facilitate the removal of some amount of the toxin before its absorption [Lehane & Lewis, 2000]. In 40% of patients, the elimination may proceed through vomiting, whereas in 20% of patients through diarrhea. The application of activated charcoal serves this purpose as well. Since gastrointestinal disorders are accompanied by a substantial loss of fluids, patients should be supplemented. In a number of patients, an improvement has been reported after the administration of antihistaminic drugs. Although the mechanism remains unexplained, the intravenous application of 20% mannitol alleviates the neurological and muscular symp-

toms without affecting the gastrointestinal disorders [Asaeda, 2001].

In addition, such activities as gutting fish containing ciguatoxin may cause itching of palms, whereas consumption with hands is likely to evoke altered gustatory sensations and dysphagia. It indicates that ciguatoxin is capable of penetrating through skin and mucous membranes. Lehane & Lewis [2000] have demonstrated that ciguatoxin occurs in mother's milk and is capable of penetrating through placenta and affecting the fetus. Transmission of that toxin through the genital tract, accompanied by algetic manifestations of the sex organs, has been reported as well.

Other toxins

Fish belonging to such species as mackerel, triggerfish, filefish as well as crabs or shrimps, feeding on colonies of marine anthozoa of the genus Zoanthus, are likely to contain palytoxin [Gleibs *et al*., 1995]. Palytoxin is considered to be one of the stronger marine toxins characterized by extremely high toxicity to mammals. Its LD_{50} values range from 10 to 100 ng/kg, whereas higher LD_{50} values have only been reported for bacterial toxins [Vick & Wiles, 1975]. Outbreaks of plytoxin poisoning seems restricted to tropical insular areas of both the Pacific and the Caribbean. Seasonality of the poisoning is often mentioned in the literature and it seems to be related to heavy rains. In many reports the viscera has been suspected to be the most toxic part. Onuma [2001] lists 27 outbreaks in the literature up to 1962. Additional reports have appeared since then. Activity of palytoxin consists in enhancing the permeability of cellular membranes for cations, mainly of sodium, potassium and calcium. Multiple functions of a cell depend of fully controlled permeability of a membrane for those elements, and its disturbance poses severe hazards.

The most rapidly occurring effect of the toxic activity of palytoxin on the body is a contraction of blood vessels and a rapid increase in blood pressure in heart and lung vessels. Damage to red blood cells is observed as well. This leads to a substantial depletion of oxygen in the body and, consequently, to suffocation.

Poisoning may also be induced by compounds naturally occurring in fish, as in the case of consuming such fish as: oilfish (*Ruvettus pretiosus*), rudderfish (*Centrolophus* sp., *Tubia* sp.) or escolar (*Lepidocybium flavobrunneum*). The above-mentioned fish species are characterized by a high content of oil (generally between 14%–25% of wet mass in the fillet). Only in two of them, i.e. escolar and oilfish, the major component of the oil are indigestible wax esters (>90%). Rudderfish species also contain similar proportions of oil, but not the indigestible wax esters seen in escolar and oilfish. In this wax esters, C14–C22 fatty acids are esterified with fatty alcohols of similar chain length. The wax esters will remain in the cooked fish if the preparation is not performed properly. For this reason, consumption of these fish may be linked with the occurrence of undesirable symptoms, including yellow-orange diarrhea with a different extent of intensity and often oily nausea, vomiting and such skin lesions as rash, reddening and itching. Most of the symptoms appear 2.5 h after consumption, on average, and their regression is observed within 24 h. Patients with chronic diseases of the gastrointestinal tract, those with malabsorption syndrome and pregnant women may be in a high risk group for the occurrence of these symptoms.

Some fish, such as orange roughy, have very high oil content just below the surface of the skin. Removal of skin and superficial flesh ("deep skinning") may remove the offending oil portion, leaving a more palatable fish. At present, it is not known whether the wax ester is evenly distributed troughout the flesh of escolar, or lies just below the surface of the skin. Hence, it is uncertain whether the wax esters can be removed by "deep skinning" of escolar and/or oilfish [Berman *et al.*, 1981].

There is a problem of improper identification and labeling of the above-mentioned fish species in the entire supply chain, hence, companies and consumers are unaware of potential problems linked with their consumption. For this reason, individuals consuming these fish for the first time should begin from a small ration to determine their own sensitivity.

Another risk is posed by the serum of eel that contains ichtiotoxin – a poison with effects resembling that of snake venom. Hence, caution should be exercised while gutting and cleansing an eel so that its blood does not reach an open wound or mucous membranes, *e.g.* ocular conjunctivia, as it may induce dangerous intoxication. In mammals, it produces contractions of the muscles, paralyses cardiac and pulmonary activity, leads to decomposition of red blood cells and diminishes blood coagulability. Once heated to a temperature of 58°C, it loses its toxic properties and is subject to decomposition.

TOXINS OF CRUSTACEA AND SHELLFISH

Regulation concering toxins in crustacea and shellfish

According to the Regulation (EC) No.852/2004 of the European Parliament and of the Council of the 29 April 2004 laying down specific hygienic rules for food of animal origin), companies of the food sector are obliged to undertake such measures so that live mussels intended for human consumption introduced into the market are in compliance with microbiological criteria, and do not exceed the limits for marine biotoxins. The latter are toxic substances accumulating in seafood as a result of their intake of toxin-producing plankton. Shellfish feed through the filtration of vast amounts of water, hence, phytoplankton, as well as bacteria and viruses, accumulate in them in high concentrations. The risk posed by the consumption of shellfish depends on the occurrence and composition of toxic algae and pathogens in the areas of shellfish maturation.

Paralytic shellfish poisoning (PSP)

The most important toxin responsible for paralytic shellfish poisoning is saxitoxin. Around 18 analogs of saxitoxins have been isolated that may induce poisoning in humans. Paralytic shellfish poisoning occurs periodically, usually after the consumption of toxin-containing shellfish, *i.e.* mussels, scallops or oysters. The periodicity of toxin occurrence results from the seasonal development of dinofllagellates, among others, *Protogonyaulax* sp. and *Alexandrium tamarense*, that constitute food to the shellfish [Novak, 1998]. They absorb active toxins or non-toxic form with food, and the latter are hydrolyzed in the gastrointestinal tract of the

shellfish to the active forms [Isbister & Kiernan 2005; Watters, 1995]. Saxitoxin and its derivative, *i.e.* gonyatoxin, block sodium channels susceptible to tetrodotoxin, thus blocking Na^+ penetration to the cells' interior, which disturbs nervous conductance and leads to motor and sensory nervous abnormality [Isbister & Kiernan, 2005].

The time span from the consumption of toxin-containing shellfish to the onset of clinical symptoms is usually 1 h (from 30 min to 3 h) with a rapid appearance of paralysis and respiratory insufficiency in severe cases. Intensification of the symptoms is linked with the extent of poisoning, .

The symptoms include gastrointestinal disorders appearing in the first 30–60 min, followed by sensation disorders manifested by pinching and numbness of tongue and lips which, with time, expands to the face, neck, fingers and toes. Patients are also likely to suffer from vertigo. In patients with weak or moderate poisoning, the symptoms are observed to regress within 2–3 days, whereas in severe cases they may last up to a week. In most fatal cases, death occurs within the first 12 h [Lehane, 2001; Meier & White, 1995].

In the case of paralytic shellfish poisoning, adjunct therapy is applied as in the case of intoxication with tetrodotoxin [Isbister & Kiernan, 2005].

In compliance with the Regulation (EC) No. 852/2004, the limit for paralytic toxin accounts for 800 μg /kg of edible parts of shellfish (in the entire body or any edible part separately).

Neurotoxic shellfish poisoning (NSP)

Poisoning occurs after consumption of shellfish containing brevetoxin produced by dinofllagellates *Karenia brevis.* That toxin demonstrates poisonous properties towards humans, marine mammals, birds and fish, but it has no influence on crustacea. Its effect on an organism consists mainly in the stimulation of sodium channels in the cell wall [Novak, 1998]. Sayer *et al*. [2005] have demonstrated that brevetoxin induced DMA damage in human lymphocytes, which points to a risk of damage of the immune system.

Symptoms appear within a few minutes up to several hours and include gastrointestinal disorders as well as sensation disorders in the form of pinching and numbness of lips, tongue and throat. Vertigo, muscular pains and alternating sensation of warmth and cold are also likely to occur. No fatal cases have been reported in the case of poisoning with that toxin [Hughes & Merson, 1976].

Amnesic shellfish poisoning (ASP)

Amnesic shellfish poisoning, also referred to as encephalopathic shellfish poisoning, results from the consumption of mussels, scallops or crabs containing domoic acid. Numerous deaths of marine birds and mammals have been attributed to the consumption of fish containing that acid [Vale & Sampayo, 2001]. Domoic acid is a water soluble, thermostable amino acid produced by microscopic alga of the genus Nitzschia [Isbister & Kiernan, 2005]. Its activity is based on the inhibition of adenyl cyclase activity in cellular membranes [Nijjar & Grimmelt, 1994] and changes in the structure of myelin sheath of axons [Schmued & Slikker, 1999].

Domoic acid demonstrates neurotoxic, immunotoxic and genotoxic activity [Dizer *et al.,* 2001]. Its neurotoxic properties are manifested by neuronal degeneration and necrosis of hippocampus regions and amygdala region. Apart from such ailments as nausea, vomiting or diarrhea, patients complain of headaches and disorientation. Symptoms of poisoning with this toxin persist for several days, although short-term amnesia can be permanent [Slikker *et al*., 1998; Jeffery *et al*., 2004].

In accordance with the Regulation (EC) No. 852/2004, limits for the amnesia-inducing toxin account for 20 μg of domoic acid/kg edible parts of shellfish (in the entire body or any of its edible parts separately).

Diarrheic shellfish poisoning (DSP)

The consumption of scallops and mussel may invoke diarrheic shellfish poisoning in humans, since they can accumulate toxins inducing diarrhea and those demonstrating cytotoxic activity. This group of toxins includes okadaic acid and its derivatives, dinophysistoxins as well as pectenotoxins and yessotoxins. These toxins, produced by dinofllagellates, *i.e. Dinophysis* sp. or *Prorocentrum* sp., accumulate in shellfish for which they constitute a source of food.

Okadaic acid is a strong inhibitor of phosphatases, enzymes closely linked with metabolic processes in cells. Phosphorylation and dephosphorylation of proteins, run by those enzymes, are very important processes proceeding in eucaryotic cells. They regulate, among others, such processes as: metabolism, membraneous transport and secretion or cell division. Diarrhea in humans is suggested to be induced by excessive phosphorylation of proteins that control the secretion of sodium through the cells of intestinal epithelium [Hallegraeff *et al*., 1995].

In contrast, pectenotoxins and yessotoxins, two other toxins enumerated in the DSP group demonstrate a small ability to induce diarrheas. In addition, pectenotoxins exhibit hepatotoxic properties, whereas yessotoxins exhibit cardiotoxic properties.

Symptoms, appearing within 5–6 h, include vomiting preceding diarrhea, stomachache and fever. Intensification and duration of the symptoms are directly linked with the amount of toxin absorbed in the gastrointestinal tract. Usually, the subsidence of symptoms is observed within 1–3 days both with and without treatment [Novak, 1998].

In compliance with the Regulation (EC) No. 852/2004, limits for okadaic acid, dinophysistoxins and pectenotoxins account for a total of 160 μg equivalents of okadaic acid/kg, whereas for yessotoxins – for 1 mg of yessotoxin equivalent/kg edible parts of shellfish (in the entire body or any of its edible part separately).

Azaspiracid shellfish poisoning (ASP)

In the course of this disease, symptoms occur which approximate those reported at DSP, yet investigations have shown that concentrations of okadaic acid and its derivatives are low and no organisms producing those toxins were observed at that time. This toxin has been detected in mussels, oysters, scallops or cockles [Hess *et al.,* 2003].

ASP symptoms include nausea, vomiting, severe diarrhea and contractions of abdominal cavity organs [Satake *et al.,* 1998].

In accordance with EU Directive No. 852/2004, limits for azaspiric acids account for 160 μg of azaspiric acid equivalents/kg of edible parts of shellfish (in the entire body or in any of its edible part separately).

Toxin level monitoring in shellfish

The Regulation (EC) No. 852/2004 of the European Parliament and of the Council of the 29 of April 2004, enacting specific hygienic rules for food of animal origin, lays down guidelines for the monitoring of toxin levels in shellfish. Samples are collected, as a rule, once per week in periods when catching is permissible. This frequency may be limited in specified areas or in respect to selected genera of shellfish, if hazard analysis in terms of toxin or phytoplankton occurrence implies a low risk of occurrence of events toxic in character. This frequency may be increased when such an analysis suggests that a weekly collection of samples is not sufficient. This evaluation should be revised periodically in order to analyze the risk of toxin occurrence in live mussels originating from these areas.

In the case of monitoring phytoplankton, samples are representative for a column of water and provide information on the occurrence of toxic species as well as tendencies proceeding in the population. Once the tendencies detected in toxic populations are indicative of toxin accumulation, the frequency of shellfish sample collection should be increased or preventive closures of these areas should be carried out until the results of toxin analysis have been obtained.

If the results of sample analysis indicate that health norms for the shellfish have been exceeded or that another threat to human health has occurred, a competent authority must close a given productive area, thus preventing the catching of live mussels. The competent authority may re-open a closed production area only if the health norms for the shellfish are again in compliance with the regulations of the EC legislation. In the case of closing a productive area by a competent authority due to the occurrence of plankton or excessive levels of toxins in the shellfish, the re-opening of this area requires two consecutive results below the boundary values specified by the regulations, in an interval of at least 48 h.

CONCLUSIONS

Toxins occurring in fish, crustacea and shellfish might be the cause of a variety of intoxications, sometimes very dangerous for human health. Most cases are characterized by mild neurological symptoms and gastrointestinal disorders. But some of intoxications might be fatal to humans, and mortality may exceed 50% cases of intoxications [Siokorski, 2004]. Those dangers prompted the Regulation of the European Parliament No. 853/2004 which introduced restrictions with regard to consuming poisonus fish and limits of marine biotoxins in crustacea and shellfish.

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TOKSYNY WYSTĘPUJĄCE W RYBACH, SKORUPIAKACH I MIĘCZAKACH – ARTYKUŁ PRZEGLĄDOWY

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Powszechnie wiadomo, że ryby są wartościowym składnikiem diety człowieka, albowiem są cennym i pożądanym źródłem białka oraz wielonienasyconych kwasów tłuszczowych. Skorupiaki i mięczaki spożywane są głównie ze względu na swoje wartości sensoryczne, poza tym mają podobne wartości odżywcze, jak również zawierają cynk usprawniający funkcjonowanie układu nerwowego. Jednakże ryby, skorupiaki i mięczaki mogą stanowić ryzyko dla zdrowia konsumenta, bowiem zawierają różne toksyny. A ryzyko to potęguje fakt, że toksyny te są często termostabilne i nie mogą zostać wyeliminowane poprzez takie zabiegi jak gotowanie.