JOINT FAO/WHO

EXPERT MEETING ON THE

Public Health Risks of Histamine and other Biogenic Amines from Fish and Fishery Products

MEETING REPORT

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Public Health Risks of Histamine and other Biogenic Amines from Fish and Fishery Products

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WORLD HEALTH ORGANIZATION

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DECLARATIONS OF INTEREST

All participants completed a Declaration of Interest form in advance of the meeting. Two of the 14 experts who participated in the meeting declared an interest in the topics under discussion.

Dr Fletcher is an ongoing employee of the New Zealand Institute for Plant & Food Research Limited. This company is a government-owned research organization which also undertakes commercial activities including conducting research and providing scientific advice to the private sector. Dr. Fletcher is engaged in carrying out independent research and providing expert advice on seafood, including the

food safety risks of histamine, and received more than US $1 000 but less than US $10 000 per year as remuneration from commercial entities in respect of his activities. Our legal advisors considered that the outcome of this meeting may lead to the development of Codex standards, and that this may have a direct or indirect commercial impact on the New Zealand Institute for Plant & Food Research.

Mr Nolte is an ongoing employee of Connors Clover Leaf Seafoods Ltd, the Canadian subsidiary of Bumble Bee Foods, which is a commercial seafood manufacturer. He is engaged in quality assurance of seafood and ongoing projects, including hazard analysis and critical control point (HACCP) assessment for tuna processing, which also address histamine. Again it was considered that the outcome of this meeting may lead to the development of Codex standards, which may have a direct or indirect commercial impact on Connors Clover Leaf Seafoods Ltd.

In light of the above, the involvement of Dr Fletcher and Mr Nolte in the meeting was limited in so far as they did not participate in the decision-making process relating to the development of meeting recommendations.

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Executive summary

Scombrotoxin fish poisoning (SFP) (often called "histamine poisoning") is caused by ingestion of certain species of marine fish that contain high levels of histamine and possibly other biogenic amines. Codex Alimentarius through its standards and guidelines aims to provide countries with a basis on which to manage issues such as histamine formation. Several of the existing standards include maximum levels for histamine in different fish and fishery products. The need to harmonize such limits and produce the associated guidance on the relevant sampling plans and other aspects of sampling resulted in the 31st Session of the Codex Committee on Fish and Fishery Products (CCFFP), which agreed to look into the issue of histamine limits in more detail. The Committee established an electronic Working Group in order to facilitate this work and identified the need for scientific advice from FAO and WHO to support this work.

FAO and WHO convened an expert meeting at the FAO headquarters in Rome from 23 to 27 July 2012 to address the public health risks of histamine and other biogenic amines from fish and fishery products. This report summarizes the outcome of that meeting.

Histamine is produced by bacterial actions, e.g. spoilage and fermentation, in fish species which have a naturally high level of the amino acid histidine. Generally, this takes place at a temperature of more than 25°C over a period of more than 6 hours or for longer at lower temperatures.

A hazard identification process, in which all biogenic amines were considered, concluded that there is compelling evidence that histamine is the most significant causative agent of SFP and that histamine can be used as an indicator of SFP. There are no difficulties in analysing histamine and a number of suitable methods are available. The different species of fish that are reportedly responsible for SFP were

identified, including those with a high histidine level which have the potential to cause SFP. Noting that this information should be easily accessible to support risk-based approaches to SFP management, the expert meeting developed the most comprehensive list of fish associated with SFP to date.

The hazard characterization concluded that a dose of 50 mg of histamine, which is the no-observed-adverse-effect level (NOAEL), is the appropriate hazard level. At this level healthy individuals would not be expected to suffer any of the symptoms associated with SFP. In addition, no cumulative effect of consecutive meals containing fish was expected, because histamine usually leaves the body within a few hours.

Using the available fish and fishery products consumption data combined with expert opinion, the meeting agreed that a serving size of 250 g captured the maximum amount eaten in most countries at a single eating event. Based on the hazard level of 50 mg of histamine and the serving size of 250 g, the maximum concentration of histamine in that serving was calculated to be 200 mg/kg. When food business operators apply good hygienic practices (GHP) and hazard analysis critical control point (HACCP), an achievable level of histamine in fish products was reported to be lower than 15 mg/kg, based on data made available by industry (using a test method with a lower detection limit of 15 mg/kg).

Recognizing that the purpose of testing is not to control the problem of SFP, but rather to verify that all the necessary control measures have been implemented effectively, identify failures in the system and remove implicated products from the market, different sampling approaches and associated plans were presented. In order to provide more explicit guidance on sampling approaches the meeting analysed a range of sampling plans implemented under different scenarios of histamine levels, as defined by the log-transformed mean and standard deviation. Examples of attributes sampling plans appropriate to different levels of tolerance for samples above 200 mg/kg, and for different assumptions about the standard deviation of histamine concentration within lots, were presented. The sampling plans shown were two-class plans and they indicate the number of analytical units required to be tested in order to have 95 percent confidence that the batch as a whole satisfies the desired specified low proportion of samples (such as 1 in 10 000) to exceed 200 mg/kg. The spread of contamination levels in the batch (i.e. the log-transformed standard deviation of contamination levels) has a strong effect on the tolerable average contamination level and, thus, on the number of samples that must be tested to "accept" the batch. Appropriate selection of the criterion against which test units comprising the sample will be assessed for compliance (the *m* value), can considerably improve the time- and cost-effectiveness of sampling:

requiring the lowest number of samples to be tested to achieve the same level of confidence about the disposition of the lot being assessed.

The expert meeting concluded that histamine formation and SFP can be easily controlled. The risk from SFP is best mitigated by applying basic GHPs and, where feasible, a HACCP system. Appropriate sampling plans and testing for histamine should be used to validate the HACCP systems, verify the effectiveness of control measures, and detect failures in the system. Sensory evaluation remains a highly useful tool for quality control programmes, but acceptable sensory quality cannot be taken as final assurance of low histamine, nor can low histamine be taken as final assurance that fish is not decomposed. As a result the conclusion of the expert meeting was to focus their advice on histamine limits and related sampling plans to those focused on consumer protection.

Several areas in which further research will be needed have been identified, including the need to clarify the critical role played by histamine and other biogenic amines in the pathogenesis of SFP.

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Acknowledgements

The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) would like to express their appreciation to all those who contributed to the preparation of this document through the provision of their time and expertise, data and other relevant information and by reviewing the document and providing comments.

Appreciation is also extended to all those who responded to the call for information that was issued by FAO and WHO and thereby drew our attention to references that were not readily available in the mainstream literature and official documentation.

The preparatory work for and implementation of the expert meeting, and the preparation of this report were coordinated by the Joint FAO/WHO Secretariat. This included Sarah Cahill, Vittorio Fattori, and Iddya Karunasagar, in FAO, and Mina Kojima in WHO. Final language editing was undertaken by Ms Sarah Binns; cover design and layout was provided by Ms Joanne Morgante.

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1

Introduction

1.1 BACKGROUND

Scombrotoxin fish poisoning (SFP) (often called "histamine poisoning") is caused by ingestion of certain species of marine fish that contain high levels of histamine and possibly other biogenic amines. The fish species involved include tuna, which accounts for 8 percent of globally traded fish. Other pelagic species such as mackerel, sardines and anchovy, which account for significant global fish production, can also be involved. These fish species contain high levels of free histidine in their tissues and when conditions are favourable for bacteria to multiply in fish, e.g. when fish are subjected to temperature abuse during and/or after harvest, bacterial decarboxylation of histidine leads to histamine formation. Other biogenic amines produced during bacterial growth in fish may potentiate the effect of histamine. The severity of the symptoms can vary, depending on the amount of histamine and other biogenic amines ingested and the individual's sensitivity to specific biogenic amines. In some parts of the world, SFP accounts for the largest proportion of cases of fish-borne illness.

Fish handling practices are critical with regard to histamine production. For the purposes of consumer protection, fish importing countries have regulations and varying limits for histamine in fish and fishery products. Failure to comply with these regulations and limits leads to import rejection and disruptions in fish trade in major international markets (Ababouch *et al.*, 2005). Thus regulations and limits related to histamine and the fish handling practices that are compatible with these are of great significance for fish producing countries.

Codex Alimentarius, through its standards and guidelines, aims to provide countries with a basis on which to manage issues such as histamine formation.

For example, the Codex Code of Practice for Fish and Fishery Products provides guidance on fish handling practices that need to be implemented to minimize food safety problems, including SFP. In addition, the Codex Alimentarius has established several standards that include maximum levels for histamine in different fish and fishery products. Different limits have been established as indicators of decomposition and as indicators of hygiene and handling. However, the associated guidance on the relevant sampling plans and other aspects of sampling is limited or even non-existent. Furthermore, many of these limits (see Annex 2) were established in an era before risk assessment and the scientific basis for the limits is unclear. As food safety management moves towards more risk- and evidence-based approaches, there is a need to review existing limits in the light of the most up-to-date scientific information and to ensure that there is a robust scientific basis for any limits recommended by Codex.

Thus, in April 2011, the 31st Session of the Codex Committee on Fish and Fishery Products (CCFFP) revisited these maximum histamine levels and agreed to look into this issue in more detail. The Committee established an electronic Working Group in order to facilitate this work. The Committee considered that it was important to the decision-making process to have available for their consideration a review of the public health risks and trade implications associated with histamine from fish and fishery products from a more general perspective. This would take into account different maximum levels in various products, existing sampling plans, and risk reductions achieved by various means at the national level. It was also agreed that the Working Group would take into account the work of the Codex Committee on Food Hygiene (CCFH) on the revision of the Principles for the Establishment and Application of Microbiological Criteria for Foods.

1.2 Objectives

This expert meeting was organized by FAO/WHO to support and facilitate this effort. Its primary objectives were:

- to review the public health impact of histamine and other biogenic amines from fish and fishery products and the trade impacts associated with histamine limits;
- to review the epidemiological and toxicological data and examine whether any risk-based control measures can be recommended for different fishery products;
- to examine the impact of a range of risk-based sampling plans for monitoring histamine levels as a marker for SFP in various fish and fishery products;
- to examine whether fish families mentioned in current Codex standards adequately cover species involved in histamine-associated illness.

1.3 Meeting approach

In order to reach these objectives the meeting decided to take a risk assessment approach and use the available data to estimate a level of histamine at which there is no observed adverse effect, estimate the exposure and characterize the risk. Consideration was also given to risk management options, including a range of sampling approaches. It was also agreed to identify those areas where the scientific knowledge was weak or limited in order to highlight areas where further research is needed.

The aim of this report is to provide the CCFFP and its working group with the scientific basis it needs to make decisions on the management of histamine in fish and fishery products.

The meeting was chaired by Dr Gerard Roessink, and Dr Ronald Benner acted as rapporteur. A group of 14 experts from 12 countries participated in the meeting in their independent capacities and not as representatives of their governments, employers or institutions. They included one expert from the fisheries industry and one expert from a government institution with commercial activities related to the fisheries industry. While these experts participated in the general discussion and exchange of information, they did not participate in the final adoption of the conclusion and recommendations of the meeting.

The deliberations of this meeting were based on three background papers, prepared in advance of the meeting by Dr P. Michael Bolger, Dr Yu (Janet) Zang, Dr Tom Ross and Dr Ronald Allen Benner. The background paper prepared by Dr Bolger and Dr Zang is available in Annex 3 and the relevant information from the papers prepared by Dr Benner and Dr Ross has been incorporated in the report.

2

Hazard Identification

2.1 BIOGENIC AMINES

2.1.1 Histamine

Histamine is a naturally occurring endogenous substance in the human body which is derived from the decarboxylation of the amino acid histidine. Histamine may also be present in certain foods containing free histidine, and is generated by certain bacteria during spoilage and fermentation of fish. Endogenous histamine has important physiological functions related to local immune responses, gastric acid secretion and neuromodulation. Histamine-rich foods may cause food intolerance in sensitive individuals and histamine contamination in fish and fish products may cause food poisoning (Taylor, 1986).

2.1.2 Cadaverine and putrescine

Cadaverine and putrescine are two other biogenic amines found in fish. Like histamine, they are produced from amino acids by bacteria during spoilage and fermentation. The precursors of cadaverine and putrescine are lysine and ornithine, respectively. Cadaverine and putrescine are both found frequently in improperly handled fish, not just those implicated in SFP, and have been studied as spoilage indicators. In some fish spoilage studies, cadaverine appeared to be formed and increased earlier than histamine (Pons-Sanchez-Cascado *et al.*, 2005; Rossi *et al.*, 2002). Although they might act as histamine potentiators (Taylor and Lieber, 1979), the contribution of these biogenic amines to SFP is not clear.

2.1.3 Tyramine

Tyramine is a naturally occurring monoamine compound derived from the amino acid tyrosine. Fresh fish contains little or no tyramine, but a large amount can be found in spoiled or fermented fish (Leuschner and Hammes, 1999; Prester, 2011).

Alhough tyramine might also act as a histamine potentiator (Taylor and Lieber, 1979), the contribution of this biogenic amine to SFP is not clear.

2.1.4 Other biogenic amines

Other biogenic amines detected in fish and fish products include spermine, spermidine, dopamine and agmatine (Park *et al.*, 2010; Visciano *et al.*, 2012). Though some of them might act as histamine potentiators (Taylor and Lieber, 1979), the contribution of these biogenic amines to SFP is not clear.

2.1.5 Microorganisms involved in biogenic amine production

Biogenic amine production requires available amino acids and amino acid decarboxylases synthesized by bacteria (EFSA, 2011). Histamine is formed in fish by certain microorganisms capable of producing the enzyme histidine decarboxylase (HDC). The histidine decarboxylases produced by these bacteria catalyse the conversion of free histidine, naturally present at high levels in the muscle of some fish, to histamine. Gram-positive and Gram-negative bacteria can both produce histidine decarboxylase but the forms of the enzymes differ (Bjornsdottir-Butler *et al.*, 2010; EFSA, 2011). In the same way, other biogenic amines (putrescine, cadaverine and tyramine) are synthesized by decarboxylases produced by Gram-positive and Gram-negative bacteria.

In the scientific literature the following species are reported to be those most likely to produce histamine: *Morganella morganii, Morganella psychrotolerans, Photobacterium damselae, Photobacterium phosphoreum, Raoultella planticola* and *Hafnia alvei* (Dalgaard *et al.*, 2008; EFSA, 2011). In the case of fermented seafood, *Staphylococcus* spp. and *Tetragenococcus* spp. are reported to be histamine producers (Satomi *et al.*, 2011; Yatsunami and Echigo, 1991). For biogenic amine compounds other than histamine, several families or genera are reported to be involved, such as Enterobacteriaceae, Pseudomonaceae, *Lactobacillus*, *Enterococcus* and *Staphylococcus* (EFSA, 2011). Within different genera or species the ability to generate histamine is very much strain dependent.

In fish, biogenic amine-producing bacteria are most likely to be present on the gills or skin, or in the gastrointestinal tract. Transfer of these bacteria to the flesh of the fish, where free amino acids may be present, leads to development of biogenic amines. Transfer can occur from the gastrointestinal tract after harvest, through migration, or via rupture or spillage of gastric contents during gutting. Microorganisms may also be transferred from the skin or gills during butchering.

The amount of biogenic amines produced depends on the level of free amino acids present, which is related to the species of fish and the amount and activity of

decarboxylase enzymes. The quantity of decarboxylases is related to the number of decarboxylase-producing bacteria transferred to the fish and the extent to which they multiply. Many conditions can affect the growth of biogenic amine producers. Temperature is the main determinant. Biogenic amine concentrations thus depend on the combined influence of time and temperature: longer times and higher temperatures will lead to greater microbial growth and biogenic amine formation. Other important factors can be involved, including pH, salt, oxygen availability and competition with other spoilage microorganisms.

In summary, the content of biogenic amines in fish products will depend on: (i) the type of fish (i.e. the amount of free amino acids), (ii) the way the fish is handled (i.e. the potential for bacterial growth in the fish products) and (iii) the duration, conditions and temperature of storage of the fish. This combination of factors can lead to highly variable levels of contamination within individual lots of fish, and even within individual fish, and has implications for the efficacy of testing schemes to assess the safety of fish and fish products with respect to histamine contamination.

2.2 TOXICOLOGICAL ASPECTS

2.2.1 Histamine

2.2.1.1 Absorption, distribution, metabolism and excretion

Human subjects can tolerate up to 180 mg of pure histamine orally without having noticeable effects, while intravenous administration of 0.007 mg of histamine produces vasodilatation and an increase in heart rate (Weiss *et al.*, 1932). This difference suggests that histamine is not efficiently absorbed from the gastrointestinal tract. It has been postulated that histamine metabolizing enzymes present in the intestinal tract prevent the absorption of ingested histamine into the circulatory system (Taylor, 1986).

Endogenous histamine is generated in mammals by the enzyme histidine decarboxylase (HDC), which is only synthesized as necessary and is degraded immediately when sufficient histamine has been generated. The HDC exists primarily in mast cells, basophils, enterochromaffin-like cells in gastric mucosa and histaminergic neurons. Generally, histamine is stored as a histamine–heparin complex in the secretory granules in these cells, and is released upon stimulation to exert its physiological functions. However, recently it has been found that a small amount of histamine is synthesized in some epidermal cells and released immediately (Shahid *et al.*, 2009).

In humans and experimental animals, histamine is primarily metabolized by two enzymes: diamine oxidase (DAO) and histamine-N-methyltransferase (HMT)