CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 14 **CX/FFP 12/32/14**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON FISH AND FISHERY PRODUCTS

Thirty-Second Session

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DISCUSSION PAPER HISTAMINE

Prepared by Japan and United States of America

Background

1. The Codex Alimentarius has established several standards which include maximum levels for histamine in different fish and fishery products. Different limits have been established as indicators of decomposition and as indicators of food safety (see Annex1). General guidance for sampling strategies were provide by Codex General Guidelines on Sampling. The histamine limit for food safety (200 PPM) was established based on member country review of the relevant scientific studies at the time; however, Codex has never performed a formal risk assessment to confirm the scientific basis for this limit. There are differences between the established limits to indicate decomposition and those that indicate a food safety risk, and this is appropriate because commodity standards must cover both food safety and essential quality criteria. As food safety management moves towards more risk and evidence based approaches, there is a need to review existing limits in light of the most up to date scientific information and ensure there is a robust scientific basis for any food safety limits recommended by Codex.

2. In April 2011, the 31st Session of the Codex Committee on Fish and Fishery Products (CCFFP) revisited the histamine maximum level for the Codex Standard for Fish Sauce and agreed to look into the general issue in more detail. The Committee agreed to establish an electronic Working Group in order to facilitate this work, however because the Report of the Joint FAO/WHO Expert Meeting on the Public Health Risks of Histamine and Other Biogenic Amines from Fish and Fishery Products was not released until September 2012, an electronic working group was not established prior to 32nd Session of the CCFFP. The Committee considered that it was important for their decision making purposes 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, taking into account different maximum levels in 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. This is due to the fact that histamine could be considered as a metabolite of microbiological activity, therefore fall into the scope of microbiological criteria defined in the Principles for the establishment and application of microbiological criteria for foods *(CAC/GL 21 – 1997).* This document is currently being revised by CCFH.

3. In order to provide scientific advice for the CCFFP working group on histamine in fish products, WHO and FAO assembled a group of experts which met at the FAO headquarters in Rome from 24 – 27 July 2012. 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 is weak or limited in order to highlight areas where further research is needed.

4. The meeting provided the CCFFP and its working group with some scientific basis needed to help make decisions on the management of histamine in fish and fishery products and identified areas of uncertainty that need more work.

Issues highlighted

5. The hazard identification, where all biogenic amines were considered, concluded that there is compelling evidence that histamine is the most significant causative agent for (scombrotoxin fish poisoning (SFP) and that histamine can be used as an indicator of SFP. Other biogenic amines may contribute to SFP, however their roll and significance is not clear at this time.

6. There are no difficulties in analysing histamine and a number of suitable methods are available.

7. 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.

8. The hazard characterization calculated that a dose of 50 mg of histamine is the no-observed-adverse-effect level (NOAEL). The Report concludes that while the NOAEL is an appropriate hazard threshold value to use for exposures in healthy individuals, this may not be the case for certain segments of the population who may have an increased sensitivity (e.g., metabolic differences, physiological conditions, drug therapies, age). In these instances a lower hazard level may need to be considered (e.g. the use of an uncertainty factor) or other specific risk management options such as fish consumption advisories should be considered. No cumulative effect for consecutive meals with fish was expected, since histamine usually leaves the body within a few hours.

9. Using the available fish and fishery products consumption data combined with expert opinion the meeting agreed that a serving size of 250 g estimated 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 concentration of histamine corresponding to the NOAEL in that serving was consequently calculated to be 200 mg/kg fish flesh.

10. 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 15mg/kg, based on data made available by industry (using a test method with a lower detection limit of 15 mg/kg).

11. 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 effectively implemented, 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. Example 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 indicate the number of analytical units required to be tested in order to have 95% confidence that the batch as a whole satisfies the desired specified low proportion of samples (such as 1 in 10000) 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 (m value), can considerably improve the time- and cost-effectiveness of sampling – requiring the least number of samples to be tested to achieve the same level of confidence about the disposition of the lot being assessed.

12. 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 programs, 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 related to consumer protection.

13. Several areas for 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.

Recommendations from the Expert meeting

14. The Expert meeting suggested the following recommendations, some of which could be relevant to the CCFFP

- In order to control histamine formation and manage the risk from SFP, fish catchers and handlers need to apply basic GHPs and the fishery industry needs to apply GHP/HACCP. It is therefore recommended that regulators and all stakeholders are aware of the basic steps required to control this hazard.
- Fishing methods should be reviewed and adapted, for example, by harvesting fish alive, to minimize histamine formation.
- To facilitate implementation of risk-based management plans, it is recommended to use the most up to date and complete information e.g. the list of fish species in this report, consumption data, epidemiological data, etc.
- To refine sampling plans, it would be desirable to better quantify the distribution of histamine levels in products and batches of products.
- Recognizing that the lower investment associated with the use of rapid histamine testing methods made them an attractive option for the industry, while also noting the importance of characterizing the performance of these methods under their conditions of use, the expert meeting recommended periodic verification of the level of performance of these methods against the reference methods.
- Epidemiological data can be used to model the dose-response assessment in addition to the existing volunteer studies model. To do so, in-depth outbreak investigations (e.g. isolating suspected biogenic amine-producing bacteria from implicated fish, testing histamine and other biogenic amine levels in remaining food samples, and estimation of consumption volume) should be encouraged.
- It is recommended that information about SFP outbreaks should be shared internationally. An international SFP alert through an existing emergency network e.g. INFOSAN[1] is recommended.
- It is recommended to develop risk-management recommendations based on the outcomes of the expert meeting. In particular, give consideration to the elaboration of risk-based sampling plans and histamine criteria.
- The experts acknowledged the utility of having access to the mathematical tools used in this meeting to develop different sampling plans. The group therefore recommended that FAO/WHO find ways to make these available in an easy to use format.

Recommendation to CCFFP

15. It is recommended that CCFFP should consider establishing an inter-session EWG to study the Expert Report and make any recommendations for Commodity Standards and Codes of Practice, related to the public health risks of histamine.

16. CCFFP should consult with CCFH in light with the revision of Microbiological Criteria.

[1] The International Food Safety Authorities Network (INFOSAN) was developed by the World Health Organization (WHO) in cooperation with the Food and Agriculture Organization of the United Nations (FAO), to promote the exchange of food safety information and to improve collaboration among food safety authorities at national and international levels.

Annex 1 - Histamine limits and sampling plans in current standards for fish and fishery products

Codex Standard	Histamine limit	Sampling Plan
Codex Stan 94- 1981 Rev 2007. Codex Standard for sardines and sardine –type products. Codex Stan 70-1981 Rev 1995 Codex Standard for canned tuna and bonito Codex Stan 119- 1981 Rev 1995. Codex Standard for canned finfish Codex Stan 244-2004 Standard for salted Atlantic herring and salted sprat	3. **Essential composition and quality factors** **3.3. Decomposition** The products shall not contain more than 10 mg/100 g of histamine based on the average of the sample unit tested **1. Hygiene and handling** no sample unit shall contain histamine that exceeds 20 mg per 100 g	Sampling of lots for examination of the final product as prescribed in Section 3.3 shall be in accordance with the FAO/WHO Codex Alimentarius Sampling Plans for Prepackaged Foods (AQL-6.5) (CODEX STAN 233-1969);
Codex Stan 36-1981 Rev1- 1995. Codex Standard for quick frozen finfish, uneviscerated and eviscerated.	3. **Essential composition and quality factors** **3.4. Decomposition** The products shall not contain more than 10 mg/100 g of histamine based on the average of the sample unit tested **5. Hygiene and handling** shall not contain histamine that exceeds 20 mg per 100 g	Sampling of lots for examination of the product shall be in accordance with the FAO/WHO Codex Alimentarius Sampling Plans for Prepackaged Foods (AQL-6.5) CAC/RM 42-1977.
Codex Stan 166-1989 Codex Standard for quick frozen fish sticks (fish fingers), fish portions and fish fillets- breaded or in batter. Codex Stan 190-1995 Codex Standard for quick frozen fish fillets. Codex Stan 236-2003 Codex Standard for boiled dried salted anchovies.	3. **Essential composition and quality factors** **3.3. Decomposition** The products shall not contain more than 10 mg/100 g of histamine based on the average of the sample unit tested **5. Hygiene and handling** shall not contain histamine that exceeds 20 mg per 100 g	Sampling of lots for examination of the product shall be in accordance with an appropriate sampling plan with an AQL of 6.5.
Codex Stan 165-1989 (Rev 1- 1995) Codex standard for quick frozen blocks of fish fillet, minced fish flesh and mixtures of fillets and minced fish flesh	3. **Essential composition and quality factors** **3.3. Decomposition** The products shall not contain more than 10 mg/100 g of histamine based on the average of the sample unit tested **5. Hygiene and handling** shall not contain histamine that exceeds 20 mg per 100 g	A Table indicating sample size (number of blocks to be tested) and acceptance number in relation to lot size (number of blocks) has been provided
Codex Stan 302-2011 Codex Standard for fish sauce	**6. Hygiene and handling** The product shall not contain more than 40 mg histamine /100g of fish sauce in any sample unit tested	Sampling of lots for examination of the final product shall be in accordance with the *General Guidelines on Sampling* (CAC/GL 50-2004). A sample unit is the individually packed product (bottle) or a 1l portion from bulk containers

Appendix

The table below presents some example 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 $\log_{10}$(histamine concentration) within lots. The sampling plans shown are two class plans and indicate the number of analytical units required to be tested (and to comply with the test criterion, i.e., '*m*') in order to have 95% confidence that the batch as a whole satisfies our desire for a specified low proportion of samples to exceed 200 mg/kg. In some cases the distributions are so narrow (standard deviation is very small), that testing samples against a criterion of 100 mg/kg is meaningless because most samples could be above this limit, yet in the lot as a whole it is very unlikely that there is any unit exceeding 200 mg/kg. In this case, it would be more practical to have a higher value for *m*, e.g. 200 mg/kg. Conversely, if the standard deviation is very high, to have confidence that the lot as a whole does not contain an unacceptable proportion of samples above 200 mg/kg, many thousands of samples may be required to attain 95% confidence.

The Table also includes examples that show that appropriate selection of the value of *m* can reduce the number of samples needed to still have the same confidence in the overall quality of the lot from a consumer perspective, but also shows that while fewer samples can protect the consumer, they may also be too protective, and result in the disposal of lots that are acceptable. More samples provide better discrimination of the overall quality of the lot and work both to ensure public health and reduce wastage. This principle is evident in the Codex Sampling Plans for Prepackaged Foods (AQL 6.5) in which more samples are taken for larger lots. The consequences of wasting larger lots that are of acceptable quality justifies the additional expense involved with testing more of analytical units."

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 $\log_{10}$(histamine concentration) within lots.

Log Standard Deviation (SD, assumed)	***Level of protection (allowable probability of any sample in the lot exceeding 200 mg/kg, risk manager's decision)***	***Mean histamine level (the maximal allowable mean in order to meet the level of protection (back-calculated from SD)***	***m* (mg/kg)***	***Percentage of analytical units allowed to have histamine levels > m***	***n ****	***c****	***Notes***
0.05	1 in 20	165	200	5	59	0	[a] In case of a small SD, a low "m" provides no discrimination—almost all samples (Italic) are allowed to exceed this "m". Therefore, a larger value of 'm' is more practical.
	1 in 20	165	100	*99*[a]			
	1 in 100	153	100	*99.99*[a]			
	1 in 1000	140	100	*98*[a]			
	1 in 10000	130	100	*99*[a]			
0.1	1 in 20	137	100	*92*[a]	2	0	[b] Increasing the number of analytical units reduces producers' risk due to false positive.
	1 in 20	137	150	35	7	0	
	1 in 100	117	100	75	3	0	
	1 in 1000	98	100	47	10[b]	1	
	1 in 1000	98	100	47	20[b]	5	
	1 in 1000	98	100	47	50[b]	17	
	1 in 10,000	85	100	24	11		
0.5	1 in 20	30	100	15	19[c]	0	[c] For a higher level of protection, a larger number of units is needed if "m" doesn't change.
	1 in 100	14	100	4	74[c]	0	
	1 in 1000	6	100	0.6	298[c]	0	
	1 in 10,000	3	100	0.09	3328[c]	0	
1.0	1 in 20	5	100	9	31	0	Using a more stringent "m" can significantly reduce the number of units need to be tested—yet providing the same level of protection.
	1 in 100	0.9	100	2	149	0	
	1 in 1000	0.2	100	0.26	1151	0	
	1 in 10,000	0.038	100	0.03	9569	0	
	1 in 10,000	0.038	50	0.09	3301	0	
	1 in 10,000	0.038	25	0.24	1239	0	
	1 in 10,000	0.038	1	7.8	37	0	

*s‘Attributes’ sampling plans are defined by several characteristics, namely:

m = the criterion against which test units[2] comprising the sample will be assessed for compliance

n = the number of test units to be tested and evaluated against the criterion (or ‘attribute’), and

c = the number of test units that are allowed to exceed the criterion ‘*m*’.

SD = standard deviation