



## Agenda Item 9

CX/FFP 15/34/10

### JOINT FAO/WHO FOOD STANDARDS PROGRAMME CODEX COMMITTEE ON FISH AND FISHERY PRODUCTS

Thirty-fourth Session

Ålesund, Norway

19 – 24 October 2015

#### DISCUSSION PAPER ON HISTAMINE

*(Prepared by Japan and the United States of America)*

#### BACKGROUND

1. CCFP33 agreed to establish an electronic working group (EWG) with the following terms of reference:
  - I. Review existing histamine related guidance in the *Code of Practice for Fish and Fishery Products* (CAC/RCP 52-2003) and any guidance documents used in member countries to decide whether the current Code is sufficient for histamine control guidance.
  - II. Consider inclusion of the susceptible species list contained in Table 2.3 of the Joint FAO/WHO Expert Meeting.
  - III. Continue to consider the application of an uncertainty factor and the safety limits for histamine in the standards for fish and fishery products and make recommendations on these limits, and to consider other risk management options, e.g. consumer advice, and whether there was a need for the decomposition limits in the standards.
  - IV. Continue to consider appropriate sampling plans for histamine.
2. A total of 29 countries and observers registered to participate in the working group (see Appendix II for the list of participants).
3. The Report is subdivided into four sections (Control Guidance, Susceptible Species, Safety Limit, and Sampling Plans) based on the EWG's terms of reference listed above. Each section contains a background, discussion, and recommendations.
4. A summary of the discussion during the EWG which provides the basis for this discussion paper is provided in the Appendix I.

#### Terminology

5. This paper follows the usage of the terms 'histamine' and 'scombrotxin' found in the *Meeting Report of the Joint FAO/WHO Expert Meeting on the Public Health Risks of Histamine and Other Biogenic Amines from Fish and Fishery Products; 23–27 July 2012*<sup>1</sup> (FAO/WHO Expert Report), which states in Section 2.3,

SFP [scombrotxin fish poisoning] is a worldwide food safety problem and is a common cause of fish poisoning that occurs in humans. The food poisoning is caused by heat-stable scombrotoxins, presumably arising from bacterial action in fish. Although detailed components of scombrotoxins have not been identified, it is generally accepted that biogenic amines, especially histamine, play an important role in the pathogenesis of SFP.

And, in Section 4.1,

<sup>1</sup> *Meeting Report of the Joint FAO/WHO Expert Meeting on the Public Health Risks of Histamine and Other Biogenic Amines from Fish and Fishery Products; 23–27 July 2012*. Link: <http://www.fao.org/3/a-i3390e.pdf>

Although other biogenic amines such as cadaverine and putrescine might also play a role in the aetiology of SFP, there are no dose–response data in animals or humans for these biogenic amines. In most epidemiological studies, SFP is associated with abnormally high histamine levels in the incriminated fish. Therefore, histamine is considered the most appropriate marker of dose in this assessment.

6. Therefore, ‘scombrototoxin’ and ‘scombrototoxin fish poisoning’ are used for the subject hazard, and ‘histamine’ is used for the specific biogenic amine used to monitor and control the hazard.

## I. CONTROL GUIDANCE

### Background

7. Histamine is a bacterial metabolite that is generated by spoilage microbe enzymatic decomposition of histidine, primarily at elevated temperatures, after fish death. It is recognized that properly harvested, stored, handled, and distributed fish results in little to no histamine accumulation. In Section 6.1 of the FAO/WHO Expert Report, the experts state:

Freshly harvested scombrototoxin-forming fish typically have histamine levels below 2 mg/kg (Frank et al., 1981; Staruszkiewicz et al., 2004). In addition, food business operators that apply GHP and HACCP can achieve a histamine level lower than 15 mg/kg in fish products, based on data made available by industry (using a test method with a lower detection limit of 15 mg/kg).

8. Conversely, it requires neglect of temperature control during harvesting, storage, handling, and/or distribution to produce fish or fishery products with elevated histamine. In Section 3.1 of the FAO/WHO Expert Report, the experts state:

High histamine levels are a result of gross time/temperature abuse during handling and storage. For example, as presented in Table 3.1, skipjack tuna stored at 25 and 31 °C did not accumulate histamine to levels greater than 10 mg/kg during up to 8 hours of storage. In yellowfin tuna stored under the same conditions, histamine levels remained below 10 mg/kg for up to 6 hours of storage but histamine began to accumulate when fish were stored for longer time periods. In fact, after 10.5 hours at 31 °C, histamine levels reached 131 mg/kg (Staruszkiewicz et al., 2004). These data illustrate that the presence of histamine in fish is related to a lack of time/temperature control.

9. In Section 6.4 of the FAO/WHO Expert Report, the experts conclude that:

For most products, the risk of SFP can be suitably mitigated by rapid chilling of the raw material and maintaining the cold chain. For such products SFP will only occur when they have been subjected to gross time/temperature abuse. However, for other products, such as smoked and fermented products, other controls may be needed.

10. The previous EWG (CX/FFP 14/33/12G)<sup>2</sup> and the physical working group (PWG) held in conjunction with CCFFP33 (FFP 33 CRD 21)<sup>3</sup> recognized that good guidance on histamine control should help reduce SFP illness; therefore, they recommended that CCFFP should review the *Code of Practice for Fish and Fishery Products* to determine if control of histamine is adequately covered.

### Discussion

11. The EWG reviewed the *Code of Practice for Fish and Fishery Products* and determined that more complete guidance on scombrototoxin/histamine control should be included. Further, it was noted that harvest vessel practices and fermenting practices (other than fish sauce under development) are not covered in the Code.

### Recommendation

**Recommendation 1)** Form a dedicated EWG to revise and elaborate guidance in the *Code of Practice for Fish and Fishery Products* with the following terms of reference:

The CCFFP should:

- a) Revise, where necessary, control guidance for scombrototoxin fish poisoning, using histamine as the marker biogenic amine for control.
- b) Include where appropriate scientific information about histamine formation with the purpose of informing on the importance of time/temperature controls.

<sup>2</sup> CX/FFP 14/33/12, Link: [ftp://ftp.fao.org/codex/meetings/ccffp/ccffp33/tp33\\_12e.pdf](http://ftp.fao.org/codex/meetings/ccffp/ccffp33/tp33_12e.pdf)

<sup>3</sup> FFP 33 CRD 21, Link: [ftp://ftp.fao.org/codex/meetings/CCFFP/CCFFP33/CRDs/CRD\\_21.pdf](http://ftp.fao.org/codex/meetings/CCFFP/CCFFP33/CRDs/CRD_21.pdf)

- c) Ensure that applicable sections of the Code cover the entire food chain (harvesting, storage, handling, processing and distribution.)
- d) Incorporate into the Code, and revise if necessary, Table 2.3 (Scientific names, free histidine levels and mean annual production levels for fish associated with SFP or high free histidine levels) from the FAO/WHO Expert Report (See Recommendation 2 below.)
- e) Consider if any products with greater risk for histamine formation because of unique processing methods need specialized or revised control guidance.

## **II. SUSCEPTIBLE SPECIES LIST (Table 2.3 “Scientific names, free histidine levels and mean annual production levels for fish associated with SFP or high free histidine levels” in FAO/WHO Expert Report)**

### Background

12. Section 2.6 of the FAO/WHO Expert Report contains the following information pertinent to Table 2.3:

Table 2.3 lists fish species that have been associated with SFP or elevated levels of free histidine.

Fish in the Salmonidae family were included in this table not on the basis of free histidine content, but rather on reported illnesses of SFP-like intoxication.

The information provided in Table 2.3 is not ranked in terms of risk for individual fish species because this is challenging from a global perspective. However the meeting recognized that individual countries or regions may need to rank fish species according to their particular situation and needs.

### Discussion

13. The *Code of Practice for Fish and Fishery Products* refers to fish species susceptible to scombrototoxin or histamine formation. It would benefit readers to have a complete list of commercial fish species that are associated with SFP and/or have high histidine levels, such as Table 2.3 in the FAO/WHO Expert Report. However, it should be considered how this list should interact with current lists of susceptible fish families in fish and fishery product standards. Some working group participants recommended amendments to the title and contents of the Table, such as only including fish species with significant international trade volume, removing the column of ‘market name’, and reviewing inclusion of species with relatively low histidine (e.g. salmon.)

### Recommendation

**Recommendation 2)** Incorporate Table 2.3 (Scientific names, free histidine levels and mean annual production levels for fish associated with SFP or high free histidine levels) from the FAO/WHO Expert Report into the *Code of Practice for Fish and Fishery Products*, revising the list where necessary. Consider how the table should be formatted, and if specific data fields (e.g. histidine levels, production levels, market names) or specific species (e.g. salmon) should be included or excluded. Consider how to integrate the Table with existing susceptible species lists in fish and fishery product commodity standards. See Recommendation 1(d) (above.)

## **III. SAFETY LIMIT**

### Background

14. The risk management role of the commodity committee is explained in the “Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius” in the *Codex Procedural Manual 23<sup>rd</sup> version* (page 109). CCFFP is the risk management body responsible for recommending the appropriate histamine safety limit in seafood standards by considering the risk assessment and uncertainty discussed in the FAO/WHO Expert Report, along with other legitimate factors and options for public protection.

15. The FAO/WHO Expert Report identified 50 mg as the no observed adverse effects level (NOAEL) for histamine in humans. The following two paragraphs in the FAO/WHO Expert Report advise risk managers about the applicability and uncertainty of the NOAEL when used to determine a histamine limit:

16. Section 4.4 (brackets from Section 3.3 of Annex 3):

It is important to bear in mind that, while the NOAEL is an appropriate hazard threshold value to use for exposures in healthy subjects, this may not be the case for those members of certain segments of the population who may have an increased sensitivity (e.g. metabolic differences, physiological conditions, drug therapies). In these instances a lower hazard level may need to be considered (e.g. the use of an uncertainty factor [of 10]) or other specific risk management options such as fish consumption advisories should be considered.

## 17. Section 4.5:

This dosage level will not apply to individuals with a specific sensitivity to histamine and would not apply to children, particularly because they consume more food per unit body weight than adults. It is also important to bear in mind that the 50 mg dosage was derived from data on a small number of subjects [n=8, n=8]<sup>4</sup>, and while the variation of response appears to be reflected in the study results further studies would be most helpful in refining this threshold value.

18. The Expert Meeting used the NOAEL (50 mg) for histamine for risk characterization. Based on the consumption data the Expert Meeting agreed to use a serving size of 250 g, and noted that this can be considered as the upper value for a serving size. Based on the hazard level of 50 mg of histamine and a consumption (m) of 250 g, the maximum concentration or level of histamine (L) in that serving that would not cause an adverse effect was calculated consequently as follows:

$$L = \text{NOAEL}/m = 50\text{mg}/250\text{g} = 0.2 \text{ mg/g} = 200 \text{ mg/kg}$$

19. During the previous EWG, participants supported studying the histamine safety limit because the current 200 mg/kg limit was established before modern risk assessment, and the limit may need to be revised based on the new risk assessment in the FAO/WHO Expert Report. Some participants proposed lowering the limit to 100 mg/kg or 20 mg/kg, while other participants supported retaining the 200 mg/kg limit. Discussed were common conditions that increase histamine sensitivity (e.g. alcohol, smoking), concurrent consumption of other histamine containing foods, and the likely potentiation effect caused by co-occurring biogenic amines. There was also concern with providing a margin of protection for children. During the PWG held in conjunction with at CCFFP33, one participant suggested lowering the health-based safety limit in standards to 100 mg/kg to provide a margin of safety as a risk management decision, while another participant recommended the use of consumption advisories under the current limit.

#### Discussion

20. Some EWG participants support lowering the histamine safety limit in applicable fish and fishery product standards (other than the *Standard for Fish Sauce*) in order to provide an uncertainty or safety margin for the identified NOAEL for healthy subjects exposed to histamine, which does not take into account inter-individual variability in responsiveness in normal or average consumers typically reflected in hazard assessments, or other known and possible contributing factors to scombrototoxin fish poisoning in healthy adults, and does not account for children consuming more per body weight. In their viewpoint, the proposed safety limit of 100 mg/kg should not affect industry because industry has provided data showing that histamine levels below 15 mg/kg are readily achievable. The proposed lower limit will not and is not intended to protect individuals with high sensitivity to histamine, which is thought to be caused by genetic inability to break down histamine in the digestive tract. However, it would provide some degree of a margin of safety or protection for individual differences in responsiveness to chemicals typically found in a population of people, and extrinsic factors that may influence responsiveness such as presence of other bioamines in the fish, prescription drugs (e.g. MAO inhibitors), etc.

21. Some EWG participants support retaining the current 200 mg/kg limit because most reported illnesses, where the portion consumed was available for testing, were attributed to histamine levels above 200 mg/kg. Additionally, a lower level is viewed by some participants to have a potential negative impact on producers in warm regions where there is difficulty maintaining the cold chain. One participant did not agree with the FAO/WHO Expert Meeting determination that the identified NOAEL would not apply to children, and the participant also had the viewpoint that lowering the histamine safety limit would not have any overall effect on reducing illnesses. In their viewpoint, training programs on good handling practices (possibly via FAO/WHO) would be a better approach than changing the limit.

22. Some participants recognized a risk with a limit set near the hazard threshold based on the NOAEL for adverse effects, and recommended using consumer advisories or warning labels to protect the public. However, it was also observed that advisories are an inappropriate way to manage a hazard that is otherwise preventable. It should be noted that consuming fish provides health benefits, such as omega-3 fatty acids necessary for healthy brain development, and consumer warnings could adversely affect an industry that mostly maintains very low histamine levels.

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<sup>4</sup> Brackets were inserted in the original Report text. It contains information on the number of sample subjects (n=8) used in each of the two histamine challenge studies performed in humans. The 50 mg NOAEL level was derived from one of these studies.

23. Some EWG participants commented that CCFFP should consult the Codex Committee on Contaminants in Foods (CCCF) for advice on appropriate health-based limits based on adverse event thresholds and uncertainty. One EWG participant did not support this approach because in their opinion the question of an uncertainty factor should not be decided by a risk management committee (such as CCCF), and they suggested that it would be preferable to consult the Expert Group rather than another risk management committee. Regarding this comment, please note that the EWG mandate was to consider an uncertainty factor as a risk management option as recommended in the FAO/WHO Expert Report, and not as risk assessors.

24. There was some EWG discussion on histamine limits for products consumed in small portions; however, it remains apparent that CCFFP should first consider the appropriate limit for normal portions (as examined in the FAO/WHO Expert Report.) It should be noted that only the *Standard for Fish Sauce* would appear affected by further consideration of small portion sizes. It was discussed that histamine limits should not be raised based on portion size alone; and CCFFP should also consider the “need” for a higher limit based on the process and application of good manufacturing practices.

Decomposition limits: If the safety limit is lowered to 100 mg/kg or below, then the provisions set for decomposition and for safety would conflict and become a potential source of confusion if the established decomposition limit is not lowered or removed in conjunction with the safety provision change.

25. Histamine is widely used by governments and industry as an indicator of decomposition and temperature abuse. Some EWG participants support removing the histamine decomposition provision from standards based on a statement in the FAO/WHO Expert Report that odors of decomposition do not always reflect or correlate with histamine levels. On the other hand, some participants support a lower histamine decomposition limit because levels below 100 mg/kg indicate gross temperature abuse. It should be noted that the conclusion of the FAO/WHO Expert Meeting was to focus their advice on histamine limits and related sampling plans on applications related to consumer protection. Review of decomposition provisions in established standards would require further work to consider their intended purpose and the attributes of various chemical and organoleptic methods.

#### Recommendation

**Recommendation 3)** EWG participants did not reach consensus on support for a lower limit (i.e. 100 mg/kg) or support for the current limit of 200 mg/kg. The EWG recommends that CCFFP consider these two options for the Hygiene section of standards (other than the *Standard for Fish Sauce*.)

26. The EWG also recommends that CCFFP consider consulting the Codex Committee on Contaminants in Foods (CCCF) for advice on appropriate health-based limits based on adverse event thresholds and uncertainty presented in the FAO/WHO Expert Report.

## **IV. SAMPLING PLANS**

### Background

27. The Codex Procedural Manual indicates that the Methods of Analysis and Sampling section of commodity standards “should include, either specifically or by reference, all methods of analysis and sampling considered necessary and should be prepared in accordance with the guidance given in the section on Methods of Analysis and Sampling in the *Relations between Commodity Committees and General Subject Committees*.” The *Principles for the Establishment or Selection of Codex Sampling Procedures* in the Codex Procedural Manual provides further procedural guidance. The Codex General Guidelines on Sampling (CAC/GL 50-2004) states under the Target Audience that “These Guidelines are above all aimed at Codex Commodity Committees which select from the plans recommended in sections 3, 4, and 5 those which at the time of the drafting of a commodity standard appear to them best suited for the inspection to be made.”

28. The current histamine sampling guidance in standards may be confusing. Some standards state that “when tested by appropriate methods of sampling and examination prescribed by the Codex Alimentarius Commission, the product shall not contain histamine that exceeds 20mg/100g,” while other standards state that “...no sample unit shall contain histamine that exceeds 20mg/100g.” One standard contains a fixed sampling plan that may not be applicable to histamine. Most standards contain a statement that lots shall be sampled with an “appropriate sampling plan with an AQL of 6.5”; however, acceptable quality levels of 6.5% are only applicable to quality defects in a continuous series of lots. Sampling plans for health-based limits should not allow any sample tested to exceed the safety limit. The standards refer to Codex prescribed sampling methods, but several do not cite the *General Guidelines on Sampling* (CAC/GL 50-2004.) Other information, such as what constitutes a lot, what part of the fish to sample and the weight of the sample, are also important to include for consistent results. FAO/WHO developed the Histamine Sampling Tool<sup>5</sup> that can be used to estimate sample sizes and limits needed for the level of protection desired.

#### Discussion

29. Participants agree that HACCP-based control systems along with good harvest vessel practices and good manufacturing practices are the means to control histamine, and that lot testing is used to verify that producer HACCP-based controls are effective. In addition to testing, other verification methods may be used, such as review of HACCP records, review of competent authority oversight, and direct inspection of foreign facilities.

30. Because of sampling limitations, countries use different sampling strategies to achieve the goal desired within the constraints of available resources. The frequency of testing and the sample size may be changed based on illness reports, past sampling results, HACCP records and other available information.

31. One strategy is to test every shipment with small sample sizes, which provides some levels of assurance that a company or country is controlling the hazard, but does not assure that the individual lot is in compliance (continuous series of lots.) Another strategy is to test a low percentage of shipments with sample sizes large enough to provide a degree of statistical confidence that the individual lot is in compliance (a lot is considered in isolation.) Both approaches are justified. However, the individual lot inspection model is inherent to Codex commodity standards, and Codex standards are applicable in cases where limited information is available about producer HACCP-based controls.

32. If a defined histamine sampling plan is included in standards, it will be regarded as appropriate to determine the acceptability of lots, even in the absence of information about HACCP-based controls. Therefore, the degree of consumer protection that a proposed sampling plan provides should be considered. It has been identified that histamine sampling guidance in adopted standards is inconsistent and confusing (see Background.) This could be resolved by including a defined sampling plan, or by including more accurate and uniform guidance on selecting a sampling plan.

33. Because of the heterogeneous distribution of histamine between fish within a lot, or even different parts within a fish, sample sizes must be fairly large to provide useful information on lot compliance. Countries may select smaller sample sizes when continually assessing processor or country HACCP-based control systems because they are not determining acceptability of individual lots, but monitoring the continued acceptability of the control system. Appropriate sampling plans differ with intended purpose: 1) Safety of lot with unknown exposure history, lot compliance with standard/dispute resolution, or 2) Routine regulatory screening or HACCP verification; therefore CFFP may wish to consider including sampling plans for different purposes within commodity standards.

34. The FAO/WHO Sampling Tool (and the FAO/WHO session presentation) suggest using “little m” (criterion against which test units comprising the sample will be assessed for compliance) below the health-based safety limit “H”, in order to reduce the number of samples required. The tool provides a table and chart showing the minimum required number of samples to be tested (n) at different concentration thresholds (little m) to achieve the objectives specified by the user. In general, an increase in level of protection requires a decrease in the value of “little m” for most values of n, or an increase in the number of samples for the same value of “little m”. A lower “little m” could be considered appropriate for verification of HACCP-based control systems because the FAO/WHO Expert Report states that histamine levels over 15 mg/kg are the result of gross temperature abuse. A clear indication of inadequate producer controls.

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<sup>5</sup> Link to FAO/WHO Histamine Sampling Tool: <http://www.fstools.org/histamine/>

35. Tables 1, 2 and 3 show two-class sampling plans designed with the FAO/WHO Histamine Sampling Tool for the current histamine safety limit (200 mg/kg). Please note that a low level of protection (1 in 100) was used for illustrative purposes because for more established levels of protection for health based limits (e.g. < 1 in 10,000), the Sampling Tool could not produce results for all three standard deviations selected. Please note that the Sampling Tool results depend on the assumed standard deviation. Results were generated for three different standard deviations, selected based on data in the FAO/WHO Expert Report (see standard deviation discussion below tables.) A two-class sampling plan is appropriate unless three product attribute levels have been identified (i.e. a level of marginal acceptability.)

Table 1. Standard deviation = 1.3 (log<sub>10</sub> scale)

Histamine Safety Limit 'M' (mg/kg)	Level of Protection	Confidence Level	Standard Deviation (log <sub>10</sub> scale)	'm' (mg/kg)	'c'	Sample Size 'n'
200	1 in 100	90%	1.3	30	0	50
200	1 in 100	90%	1.3	15	0	31
200	1 in 100	90%	1.3	6	0	18
200	1 in 100	90%	1.3	2	0	10
200	1 in 100	90%	1.3	1	0	7

Table 2. Standard deviation = 0.88 (log<sub>10</sub> scale)

Histamine Safety Limit 'M' (mg/kg)	Level of Protection	Confidence Level	Standard Deviation (log <sub>10</sub> scale)	'm' (mg/kg)	'c'	Sample Size 'n'
200	1 in 100	90%	0.88	55	0	50
200	1 in 100	90%	0.88	35	0	32
200	1 in 100	90%	0.88	19	0	18
200	1 in 100	90%	0.88	8	0	9
200	1 in 100	90%	0.88	3	0	5

Table 3. Standard deviation = 0.5 (log<sub>10</sub> scale)

Histamine Safety Limit 'M' (mg/kg)	Level of Protection	Confidence Level	Standard Deviation (log <sub>10</sub> scale)	'm' (mg/kg)	'c'	Sample Size 'n'
200	1 in 100	90%	0.5	96	0	50
200	1 in 100	90%	0.5	75	0	32
200	1 in 100	90%	0.5	52	0	18
200	1 in 100	90%	0.5	30	0	9
200	1 in 100	90%	0.5	17	0	5

**'Level of Protection'** is the maximum acceptable fraction of sample units from a lot allowed to exceed the 'Histamine Safety Limit'. 1 in 100 is the lowest level of protection allowed in the Sampling Tool. The 'level of protection' used for a health based limit is generally higher (e.g. 1 in 10,000.)

**'Confidence Level'** is the desired confidence level that lots that do not meet the 'level of protection' will be rejected by the sampling plan. The Sampling tool is limited to confidence levels above 90%.

**'Standard deviation' (SD):**

The lower the SD, the fewer samples are required for the same statistical power.

Table 1: SD = 1.3 (log<sub>10</sub> scale). The FAO/WHO Expert Report (Section 5.3) states that surveys where high contents of histamine were detected the standard deviation was often high (above 1.3).

Table 2: SD = 0.88 (log<sub>10</sub> scale). SD = 0.88 is the average SD (log<sub>10</sub> scale) of the 39 surveys listed in Table 5.1 of the FAO/WHO Expert Report. SD = 0.88 also agrees with the ICMSF recommended standard deviation assumption for solid foods<sup>6</sup>.

Table 3: SD = 0.5 (log<sub>10</sub> scale). The FAO/WHO Expert Report (Section 5.3) states that surveys in which no high concentration of histamine was detected, the standard deviations are comparatively low (about 0.5 or less.) This SD may be appropriate to use if presuming lots were produced under adequate histamine control.

'm': Sample concentrations higher than 'm' are counted and compared to 'c'. If the count exceeds 'c' then the lot is rejected. Note that levels below 5 mg/kg are near the method detection limit (~1 mg/kg) and are not considered advisable for a regulatory decision limit.

'c' is the acceptable number of samples above little 'm'. In the case of two-class plans, 'c' = 0.

'n' is the sample size. The Sampling Tool is limited to sample sizes ≤ 50.

36. Specific sampling plans were discussed by the EWG; however, a sampling plan cannot be developed without knowing the health-based safety limit that the plan is supposed to be designed for. For illustrative purposes, the following three sampling plans are listed with 'confidence levels' (see definition above) calculated for the current 200 mg/kg histamine safety limit. A standard deviation = 0.5 (log<sub>10</sub> scale) is used, which presumes good manufacturing controls and avoids producer risk. (Please note that the confidence levels, except for the 1 in 100 level of protection for Plan A, were outside the parameters of the FAO/WHO Histamine Sampling Tool, and were calculated independently.)

A) Fixed sample size, two-class sampling plan

n = 18; c = 0; m = 35 mg/kg

(Confidence level at 1 in 100 level of protection = 98.5%)

(Confidence level at 1 in 10,000 level of protection = 22.0%)

This plan is within the parameter limits of the FAO/WHO sampling tool, and uses a practical sample size, and a "little m" that if exceeded, clearly indicates temperature abuse and likelihood that other samples in the lot are over the safety limit. This plan may be considered marginally acceptable for determining individual lot acceptance.

B) Variable sample size, two-class sampling plan

n ≥ 5; c = 0; m = 100 mg/kg

(Confidence level at 1 in 100 level of protection = 19.4%, at n = 5)

(Confidence level at 1 in 10,000 level of protection = 0.5%, at n = 5)

This plan was proposed with n = 5, however this is changed to n ≥ 5 to indicate 'n' as a minimum sample size. This plan (at n = 5) lacks power to determine individual lot compliance, however may be appropriate for continuous monitoring of control systems.

C) Variable sample size, three-class sampling plan

n = 9; c = 2; m = 100 mg/kg; M = 200 mg/kg

--satisfactory if the following requirements are fulfilled:

1. The mean value observed is ≤ m
2. A maximum of c/n values observed are between m and M
3. No values observed exceed the limit of M

-- unsatisfactory, if the mean value observed exceeds m or more than c/n values are between m and M or one or more of the values observed are > M

(Confidence level at 1 in 100 level of protection = 8.9%, at n = 9)

(Confidence level at 1 in 10,000 level of protection = 0.1%, at n = 9)

<sup>6</sup> See Page 15 of "Relating Microbiological Criteria to Food Safety Objectives and Performance Objectives". International Commission on Microbiological Specifications for Foods (ICMSF). J.FoodCont.2008.11.005.  
Link: <http://www.icmsf.org/pdf/JFCO1631.pdf>

(Note that these confidence levels do not take into account mean  $\leq m$ , however the mean will rarely exceed 'm' without breaking the 3-class criteria)

This plan corresponds to EC regulation 2073/2005. The use of a fraction (2/9) rather than a fixed number ('c') between 'm' and 'M', and an introduction stating that each plan "shall be respected as a minimum," implies that 9 is the minimum sample size. This plan (at n = 9) lacks power to determine individual lot compliance, but may be appropriate for continuous monitoring of control systems.

#### Recommendation

#### **Recommendation 4)**

##### For the Hygiene section of standards

- The wording for the health-based histamine safety limit should be consistent among standards unless different limits apply for specific commodities.

##### For the Methods of Analysis and Sampling section of standards

- Reference the *General Guidelines on Sampling* (CAC/GL 50-2004).
  - Further expert review may be needed to determine if any particular approach within the *General Guidelines on Sampling* (CAC/GL 50-2004) should be referenced or explained in standards.
- Clarify that "AQL of 6.5" does not apply to histamine.
- Clarify the use of the defined sampling plan listed in the *Standard for Frozen Blocks of Fish Fillet, Minced Fish Flesh and Mixtures of Fillets and Minced Fish Flesh* (Codex STAN 165-7989) that may not be intended for the histamine safety limit.
- Include additional sampling guidance; such as what constitutes a lot, which part of the fish to sample, weight of the sample unit, pooling samples, etc.
- Options for sampling plan information:

Option 1: No change. Countries can select appropriate sampling plans using existing Codex guidance (considered above.) Most CCFFP standards do not include specific sampling plans for health-based, or quality, limits. Codex procedure recommends including a sampling plan. However, in order to be included in the commodity standard, the reference sampling plan used to determine acceptance of a lot (or settle disputes) should provide a measurable degree of confidence about the safety of a lot with unknown exposure history.

Option 2: Include the following reference to the FAO/WHO Histamine Sampling Tool:

SAMPLING, EXAMINATION AND ANALYSIS

**Sampling of lots for examination of the final product shall be in accordance with the *General Guidelines on Sampling* (CAC/GL 50-2004). The FAO/WHO Sampling Tool for Histamine (<http://www.fstools.org/histamine/Default.aspx>) provides useful information about the performance of sampling plans<sup>7</sup> under various decision parameters that may be applicable under some sampling plan strategies.**

This is optional guidance that was designed for Codex histamine sampling by FAO/WHO experts.

Option 3: Include a defined sampling plan or more than one sampling plan for different purposes.

37. In order to design justified sampling plans in a transparent manner, it is necessary to first establish an agreed health-based safety limit (discussed in Section III.) Because a health-based safety limit has not been agreed, the EWG cannot properly propose specific sampling plans. After the health-based safety limit is agreed, CCFFP may consider establishing an EWG devoted to sampling plans and related guidance.

<sup>7</sup> A sampling plan is a planned procedure which enables one to choose, or draw separate samples from a lot, in order to get the information needed, such as a decision on compliance status of the lot (CAC/GL 50-2004.)

### Summary of the Discussion in EWG (for information only)

1. The EWG received comments on the 2<sup>nd</sup> draft Discussion Paper on Histamine from nine participants (Australia, France, India, Japan, Morocco, New Zealand, Norway, Spain, and USA.) The Discussion Paper on Histamine has been revised taking into consideration the comments received.

2. The following is the summary of the discussion and the rationales of the revision of the Discussion Paper on Histamine.

#### Comment Discussion

3. The comments received during the second round did not significantly change the areas of consensus and lack of consensus identified in the Discussion Paper. The comments received were simultaneously distributed to all EWG participants, and therefore are not repeated in this circular.

4. Several comments supported particular recommendations in the Discussion Paper and did not propose any specific revisions to the Paper, therefore no revisions were made. Other comments proposed improvements or corrections to the Discussion Paper that were beneficial and did not materially change the Paper, and the revisions were made and are not discussed in this circular. Also, the EWG leads made some revisions, such as replacing certain sections with wording from the Expert Report that is not discussed. Discussed below are those comments that proposed significant revisions to the Discussion Paper where further discussion of the action taken is appropriate.

#### I. Control Guidance

##### **Background, 2<sup>nd</sup> paragraph, 2<sup>nd</sup> sentence**

5. A participant recommended removing the following sentence (from Section 6.1 of the FAO/WHO Expert Report):

“In addition, food business operators that apply GHP and HACCP can achieve a histamine level lower than 15 mg/kg in fish products, based on data made available by industry (using a test method with a lower detection limit of 15 mg/kg).”

6. In the participant’s viewpoint, the 15 mg/kg level is unfounded because several variables were not taken into account (e.g. fishing area, season, water temperature, species, processing mode, sample size, study duration.) Regarding this comment, the sentence was retained in the Discussion Paper because the details of the data were available to the Expert Meeting, and the Expert Report does not indicate that any important variables were missing. The sentence appears reasonable because the previous sentence states that “freshly harvested scombrototoxin-forming fish typically have histamine levels below 2 mg/kg” and the sentence implies that the 15 mg/kg level is only achievable by applying GHP and HACCP.

##### ***Recommendation 1), e) Consider if any product with greater risk for histamine formation because of unique processing methods need specialized or revised control guidance***

7. A participant commented that justification for higher histamine limits for certain products should not be based solely on portion size. In their viewpoint, it must be shown that higher histamine content is unavoidable due to the nature of the process under best practices. And, it should be considered what creates the “need” for higher limits, and it should not be “bad practices.” The comment proposed revising Recommendation 1) e) by adding **(excluding “bad practice”).** Regarding this comment, this section of the Discussion Paper is concerned with histamine control guidance in the Code of Practice for Fish and Fishery Products. Recommendation 1) e) concerns processes, such as smoking, salting, and fermenting, that require more complicated histamine control (i.e. monitoring additional parameters at certain steps) that may require more specialized guidance in the Code in order to avoid “bad practices”. Because the Code of Practice does not contain safety limits, the Safety Limit section of the Discussion Paper (Section III) was revised to cover discussion of small portion sizes and consideration of the “need” for higher limits as recommended in the comment.

**Recommendation 1) Form a dedicated electronic working group to revise and elaborate guidance in the Code of Practice for Fish and Fishery Products with specific terms of reference (as detailed in the 2<sup>nd</sup> Draft Discussion Paper on Histamine.)**

8. A comment recommended that the EWG terms of reference should include a call for data on histamine test results from processors and competent authorities because this data would be of value to risk managers. Regarding this comment, it should be noted that FAO and WHO already made a call for histamine data (deadline December 2011) from governments, interested organizations, health care providers, academia, veterinarians, the food industry, consumer groups, laboratories and individuals. The relevant data received is summarized in Section 3.2 (Detection frequency of histamine and levels of contamination) of the FAO/WHO Expert Report. CCFFP may be able to access the actual data submitted if needed. A new call for data would require an extensive effort to obtain data collected over the last four years and any data that was not previously submitted. The suggested addition to the terms of reference was not made because it was not clear how supplemental histamine test data would benefit the work on histamine control guidance proposed in the Discussion Paper; however it may be useful for ongoing assessment of the risk.

## II. Susceptible Species List.

**Table 2.3 in the FAO/WHO Expert Report, “Scientific names, free histidine levels and mean annual production levels for fish associated with SFP or high free histidine levels”**

### Discussion Section

9. A comment suggested removing species from the Table if their association with SFP is the result of poor practices. Regarding this comment, please note that this approach could result in removing all species listed in the Table because all fish have insignificant histamine (< 1mg/kg) when freshly caught, and development of histamine can be completely controlled by application of adequate cooling controls, although this requires adequate facilities and resources.

### **Recommendation 2)**

10. Several comments proposed recommendations to revise the table format, and to exclude or include certain table information. These comments did not all agree and they will need to be considered by the proposed COP EWG. Recommendations 1 and 2 in the Discussion Paper are revised to include consideration of revisions to the Table by the proposed EWG.

## III. Safety Limit

### **Background, 1<sup>st</sup> paragraph**

11. A comment recommended the following revision:

The risk analysis role of the ~~commodity committee~~ **Codex Alimentarius** is explained in the “Working Principles for Risk Analysis for Application in the Framework of the *Codex Alimentarius*” in the *Codex Procedural Manual, 23rd version* (page 109). CCFFP ~~is the risk management body responsible for determining the appropriate histamine safety limit in seafood standards by~~ **may recommend histamine safety limits for endorsement by CCCF** considering the risk assessment and uncertainty discussed in the FAO/WHO Expert Report, along with other legitimate factors and options for public protection.

12. In order to be precise and remain consistent with the paragraph’s purpose of providing guidance on CCFFP’s role in the risk analysis process, and because CCCF and CCFH may endorse provisions for toxins produced by microbial organisms, the paragraph was revised as follows:

The risk analysis **management** role of the commodity committee is explained in the “Working Principles for Risk Analysis for Application in the Framework of the *Codex Alimentarius*” in the *Codex Procedural Manual, 23rd version* (page 109). CCFFP is the risk management body responsible for ~~determining~~ **recommending** the appropriate histamine safety limit in seafood standards by considering the risk assessment and uncertainty discussed in the FAO/WHO Expert Report, along with other legitimate factors and options for public protection.

### **Background, 2<sup>nd</sup> paragraph**

13. A participant recommended removing the following sentence:

The FAO/WHO Expert Report identified the no observed adverse effects level (NOAEL) for histamine in humans, and determined that 200 mg/kg of histamine in fish (based on 95% of maximum average consumption) would provide a dose at the threshold of possible adverse effects in healthy adults.

14. And, replacing it with the following quote from the Expert Report:

In Section 6.1 of the FAO/WHO Expert Report, the experts state: “SFP will only occur in healthy individuals when a dose of at least 50 mg histamine is consumed and this generally infers that the fish would have histamine levels exceeding 200 mg/kg.”

15. In the participant’s viewpoint, it is not so straightforward to say “200 mg/kg would provide a dose at the threshold of possible adverse effects in healthy adults.” This viewpoint is correct because the 200 mg/kg level would only approach the hazard threshold if a large sized food portion were consumed. Therefore the “threshold” discussion was removed from the Discussion Paper and replaced with the following (“consumption” is elaborated later):

The FAO/WHO Expert Report identified 50 mg as the no observed adverse effects level (NOAEL) for histamine in humans.

16. The proposed replacement language was not included because it may be misunderstood outside of the context of the Expert Report. The language is referring to SFP-like symptoms in response to histamine, and not to scombrototoxic fish poisoning itself. The Expert Report indicates that the nature of scombrototoxic fish poison is uncertain, and that the threshold toxic dose for histamine in scombrototoxic fish poison is unknown.

### Discussion, general

17. A comment recommended that the specific fish species and fishery products to which the safety limit under discussion applies should be clarified. Regarding this comment, the EWG terms of reference were to consider “the safety limits for histamine in the standards for fish and fishery products”, and therefore the discussion applies to the applicable products and species indicated in those standards with histamine provisions. The FAO/WHO Expert Report “Table of fish associated with SFP or high free histidine levels” differs from the lists of susceptible fish in standards with histamine provisions; therefore, EWG Recommendations 1 and 2 include “Consider how to integrate the Table with the existing susceptible species lists in fish and fishery product commodity standards.” It may be decided to cite the COP Table in certain standards for consistency, which would change the applicable species. Regarding different limits for products consumed in small portions, the previous EWG (CX/FFP 14/33/12) recommended first considering products consumed in normal portions, which is the portion size considered by the FAO/WHO Expert Report. Currently, fish sauce is the only standardized product where a higher limit has been justified based on the portion size and the nature of the process, and any revisions to this standard would require further assessment of portion sizes, fermentation, and other legitimate factors. The Discussion Paper was revised to clarify that the EWG is considering the histamine safety limit in applicable fish and fishery product standards (other than the Standard for Fish Sauce.)

### Discussion, 1<sup>st</sup> paragraph

18. A comment recommended the following revision in order to more correctly represent the viewpoint of participants that support the use of a safety margin:

About half EWG participants support lowering the histamine safety limit in order to provide an uncertainty or safety margin for the ~~histamine-based illness~~ **hazard** threshold **for histamine-based illness**, which does not take into account **inter-individual variability in responsiveness in normal or average consumers typically reflected in hazard assessments, or** other known and possible contributing factors to scombrototoxic fish poisoning in healthy adults, and does not account for children consuming more per body weight. In their viewpoint, the proposed safety limit of 100 mg/kg should not affect industry because industry has provided data showing that histamine levels below 15 mg/kg are readily achievable. The proposed lower limit will not and is not intended to protect individuals with high sensitivity to histamine, which is thought to be caused by genetic inability to break down histamine in the digestive tract. **However, it would provide some degree of a margin of safety or protection for individual differences in responsiveness to chemicals typically found in a population of people, and extrinsic factors that may influence responsiveness such as presence of other bioamines in the fish, prescription drugs (e.g. MAO inhibitors), etc.**

19. The proposed revision was included in the Discussion Paper.

### Discussion, 2<sup>nd</sup> paragraph (reasons in support for the current 200 mg/kg limit)

20. One participant commented with viewpoints in support of the current limit that were not covered in the existing paragraph. Although the participant did not request a change to the Discussion Paper, the following sentences were added to the 2<sup>nd</sup> paragraph to cover these viewpoints:

One participant did not agree with the FAO/WHO Expert Report conclusion that the identified NOAEL would not apply to children, and the participant also had the opinion that lowering the histamine safety limit would not have any overall effect on reducing illnesses. In their viewpoint, training programs on

good handling practices (possibly via FAO/WHO) would be a better approach than changing the histamine limit.

### **Discussion, New paragraph**

21. One participant recommended including a paragraph to cover EWG discussion related to the EWG recommendation to consult CCCF about limits and uncertainty. Two other participants [France, NZ] also submitted comments related to this recommendation. The following paragraph was added to cover the EWG discussion:

Some EWG participants commented that CCFFP should consult the Codex Committee on Contaminants in Foods (CCCF) for advice on appropriate health-based limits based on adverse event thresholds and uncertainty. One EWG participant did not support this approach because in their opinion the question of an uncertainty factor should not be decided by a risk management committee (such as CCCF), and they suggested that it would be preferable to consult the Expert Group rather than another risk management committee. Regarding this comment, please note that the EWG mandate was to consider an uncertainty factor as a risk management option as recommended in the FAO/WHO Expert Report, and not as risk assessors.

### **Recommendation 3), 2<sup>nd</sup> paragraph**

***CCFFP may wish to consult the Codex Committee on Contaminants in Foods (CCCF) for comments on appropriate health-based limits based on adverse event thresholds and uncertainty.***

22. One participant did not support the recommendation to consult CCCF because in the participant's viewpoint an uncertainty factor should not be decided by a risk management body. Regarding this comment, the recommendation to consult with CCCF was received from an EWG participant during the 1<sup>st</sup> round and from more than one participant during the 2<sup>nd</sup> round. During the 33<sup>rd</sup> CCFFP Session (para 115, 116 in REP14/FFP), the risk management body's responsibility for deciding an uncertainty factor was made clear, and became part of the EWG mandate. Both risk assessors and risk managers may apply uncertainty factors, and the Expert Group decided to handle the uncertainty issue by advising CCFFP to consider risk management options, such as an uncertainty factor or consumption advisories.

23. Two participants recommended specific changes to the language of the second paragraph to more directly recommend consulting with CCFFP. In one participant's viewpoint, CCFFP has an option to defer determination of the appropriate safety level to CCCF. Regarding these comments, this topic was discussed during the previous session (para 114 in REP14/FFP) where it was considered that FAO/WHO had already performed a risk assessment and that further expert consultation should not be needed. However, in light of continued lack of consensus on the appropriate safety limit based on the information contained in the FAO/WHO Expert Report, it may be helpful for CCFFP to ask CCCF for advice based on their risk management experience in relation to these matters. This should not include asking for a new risk assessment, which would require new scientific information in order to be justified. The paragraph was revised as follows:

**The EWG recommends that CCFFP ~~may wish to~~ **consider** consulting the Codex Committee on Contaminants in Foods (CCCF) for ~~comments~~ **advice** on appropriate health-based limits based on the adverse event thresholds and uncertainty **presented in the FAO/WHO Expert Report.****

## **IV. Sampling Plans**

### **Discussion**

24. One comment proposed a specific sampling plan for "fishery products that have undergone enzyme ripening treatment in brine." No justification was provided, but the plan is similar to EC regulation 2073/2005 with the histamine levels increased by 200 mg/kg. It was considered unnecessary to include this plan in the Discussion Paper because consideration of such a plan would depend on exactly which Standard it would go into, and would also depend on the type of sampling guidance finally included in standards for non-ripened products.

### **Recommendation 4) Options for sampling plan information**

25. One comment recommended including an option for reduced or pooled sampling, based on historical data or when there is evidence that GMP/HACCP temperature controls are in place.

26. Regarding pooled sampling, this can be done regardless of lot history or availability of HACCP documentation. Pooling requires a lower pooled decision limit, created by dividing the normal decision limit by the number of samples in the pool. The lower limit allows detection of a single sample within the pool that is over the normal limit. The number of samples that can be pooled is limited by the normal decision limit and the method's LOQ. "Pooling samples" was added to the Recommendation 4 list of possible additional sampling guidance of the Discussion Paper (4<sup>th</sup> bullet.)

27. Regarding the recommendation to include an option for reduced sampling based on historical data or evidence that HACCP controls are in place, it should be considered that a country can always reduce the sample size for HACCP verification purposes. However, the standard's "official" sampling plan must be adequate to determine compliance of an individual lot of unknown exposure history, and it may be used in cases of disputed histamine content. Option 3 in the Discussion Paper suggests the possibility of including in standards more than one defined sampling plan for different purposes. CCFFP may wish to include an alternative (reduced sample size) plan for the purpose of regulatory verification of HACCP systems, in addition to a sampling plan for individual lot compliance or possible dispute resolution.

## LIST OF PARTICIPANTS

**Argentina**

Barbara Castellani  
bcastellani@minagri.gob.ar

Fabian Ballesteros  
fballest@senasa.gov.ar

Lic. Silvana Ruarte  
sruarte@anmat.gov.ar

Argentina Codex Contact Point  
codex@minagri.gob.ar

**Australia**

Lynda Hayden  
lynda.hayden@agriculture.gov.au

**Bangladesh**

Md.Mazharul Islam  
Rural.development.bd@gmail.com

**Brazil**

Lucio Akio Kikuchi  
lucio.kikuchi@agricultura.gov.br

**Chile**

Francoise Barbe  
fbarbe@sernapesca.cl

**Croatia**

Tanja Bogdanovic  
t.bogdanovic.vzs@veinst.hr

**Egypt**

Hoda Mohamed Fathi  
hfathi55@yahoo.com

**European Union**

Mr. Paolo Caricato  
paolo.caricato@ec.europa.eu

EU Codex contact point  
codex@ec.europa.eu

**France**

Ms Geneviève MORHANGE  
genevieve.morhange@dgccrf.finances.gouv.fr

Ms Virginie Hossen  
virginie.hossen@agriculture.gouv.fr

Mr Guillaume DUFLOS  
guillaume.duflos@anses.fr

**Ghana**

Dr. Lawrence D. Abbey  
abbeyld@yahoo.com

Mr. Meinster Bonneford Kodjo Eduafo  
keduafo@yahoo.com  
meinsterkodjoedufo@rocketmain.com

**Iceland**

**Ms Dora Gunnarsdottir**  
dora.gunnarsdottir@mast.is

Mr. Gardar Sverrisson  
gardar.sverrisson@mast.is

**India**

Dr. Satyen Kumar Panda  
satyenpanda@gmail.com

NCCP, India  
Codex-india@nic.in

**Iran**

Afsaneh Samiei  
fishcommittee@gmail.com

Yazdan Morady  
[ymorady@yahoo.com](mailto:ymorady@yahoo.com)

**Iraq**

Miss. Manal Salman Mohammed  
altaee\_manal@yahoo.com

**Japan**

Dr. Rei Nakagawa  
codexj@mhlw.go.jp

Mr. Hirohide Matsushima  
hirohide\_matsushima@nm.maff.go.jp

Ms. Tomoe MUKAE  
tomoe\_mukae@nm.maff.go.jp  
[codex\\_maff@nm.maff.go.jp](mailto:codex_maff@nm.maff.go.jp)

**Mauritius**

Mrs Madvi Jugnarain  
mjugnarain@mail.gov.mu

**Mexico**

Muncino Gabriela Brito  
gmucinob@cofepris.gob.mx

Ines Alvarez Perez  
ialvarez@cofepris.gob.mx

**Morocco**

Dr. OLEYA EL Hariri  
oleyafleur@yahoo.fr

**New Zealand**

Jim Sim  
jim.sim@mpi.govt.nz

**Norway**

Bjørn Tore Lunestad  
blu@nifes.no

Geir Olav Valset  
geir.valset@mattilsynet.no

Vigdis S. Veum Moellersen  
visvm@mattilsynet.no

**Poland**

Codex Contact Point for Poland  
kodeks@ijhars.gov.pl

**Russia**

Sergey Hotimchenko  
hotimchenko@ion.ru

**Senegal**

Dr Ibrahima Cisse  
ibrahima\_cisse@hotmail.com

**South Africa**

Mr Deon Jacobs  
JACOBSDC@nracs.org.za

**Spain**

Julian Garcia Baena  
JGBaena@magrama.es

Victoria Ruiz Garcia  
riesgosbiologicos@msssi.es

Sara Gomez Troyano  
riesgosbiologicos@msssi.es

**Sweden**

Mrs. Carmina Ionescu  
carmina.ionescu@slv.se

**Thailand**

Manat Larpphon  
manat@acfs.go.th  
mlarpphon@yahoo.com  
codex@acfs.go.th

**United States of America**

Paulo Almeida  
paulo.almeida@fsis.usda.gov

**FAO FIPM**

Karunasager Iddya  
iddya.karunasagar@fao.org