CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 5 **CX/MAS 18/39/5**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON METHODS OF ANALYSIS AND SAMPLING

39th Session
Budapest, Hungary, 7 – 11 May 2018

DISCUSSION PAPER ON THE CRITERIA FOR ENDORSEMENT OF BIOLOGICAL METHODS USED TO DETECT CHEMICALS OF CONCERN

(Prepared by the Electronic Working Group led by Chile and Mexico)

BACKGROUND

1. The Codex Committee on Methods of Analysis and Sampling, at its 35th session (March 2014) (CCMAS35) endorsed the Criteria for determination of toxin analogues by chemical methods in the section 1-8.6.1 of the *Standard for live and raw bivalve molluscs* (CXS 292 – 2008), as well as the classification of the methods AOAC 959.08 (mouse bioassay) and AOAC 2011.27 (receptor binding assay) as Type IV, in the section I-8.6.2 of that Standard.[1]

2. During CAC37 (July 2014), the draft sections I-8.6.1 and I-8.6.2, endorsed and amended by CCMAS, were considered. There was concern regarding the classification of the mouse bioassay as Type IV, which would mean that it could not be used for control, inspection and regulatory purposes. Some delegations expressed the view that the CCMAS should consider developing criteria for biological methods as the current criteria used for section of methods applied to chemical methods, and led to the Type IV classification.

3. As a result of the debate, the CAC returned section I-8.6.2 to CCMAS with a request to review the typing of the methods in question, and encouraged CCMAS to proceed rapidly with its discussion on the way to deal with biological methods from a criteria approach perspective.[2]

4. At CCMAS36 (February 2015), the request of the Commission to review the typing of the methods for determination of marine biotoxins was analyzed. After an extensive discussion on the types of methods used to quantify marine toxins (chemical and biological), the Committee agreed to maintain its endorsement of the methods in section I-8.6.2 of the Standard for live and raw bivalve molluscs as Type IV, and agreed that the development of criteria for biological methods should be considered as a matter of urgency, as also encouraged by the Commission.

5. The CCMAS established a eWG led by Chile and co-chaired by France, with the following mandate: i) classify biological methods according to their nature, principles, characteristics, etc. ii) identify to which type of the method criteria approach applies, and iii) recommend criteria to endorse each type of biological methods identified in step ii). For the purpose of this working group, biological methods are considered to be those methods of analysis that use whole or parts of organisms as analytical indicators, excluding PCR, enzymatic and ELISA. Also, the methods used for the assessment of food hygiene were beyond the scope of the eWG, which falls within CCFH competences.[3]

6. At CCMAS37 (February 2016), the Delegations of Chile and France presented the Discussion paper on criteria for endorsement of biological methods used to detect chemicals of concern, and explained that the eWG had only addressed the first item of its mandate (methods classification).[4]

[1] REP14/MAS, para. 23-25
[2] REP14/CAC, para. 53 - 60
[3] REP15/MAS, para. 44 - 59
[4] CX/MAS 16/37/6

7. The eWG noted that most of the biological methods classified in Codex are Type II and III, with only one Type I method (mouse bioassay for determination of the protein efficiency ratio), while the methods for determination of marine biotoxins are Type IV. In addition, it was considered as an obstacle the lack of revision of the list of methods in CXS 234-1999, because there are no longer provisions for some of them, and could be removed or considered by the Committee (e.g. methods for minarine and margarine, as well as the current use of chromatographic methods for the determination of vitamins).

8. During the session, a general discussion was held, and it was supported the proposal to clean up the list of biological methods, seeking guidance from the relevant committees.This, to identify what kind of methods the criterion would apply and to avoid defining criteria for methods which might be removed from the list.

9. During CCMAS38 some countries pointed out that no more discussion about the criteria for endorsement of biological methods is necessary, because the use of biological methods was replaced by HPLC methods. Others mentioned that biological methods are included in the approved methods in the CODEX system and some other methods might be included, and also for the review of CXS 234, it would be necessary to know how to accept those methods.

10. Delegates in favour of developing specific criteria for endorsement of biological methods considered that the General Criteria were not applicable to biological methods. However, delegates opposing, pointed out that General Criteria for selection of Methods of Analysis were also applicable to biological methods, and in case of numeric criteria were needed, then a case-by-case consideration should be carried out.

11. Finally, the Committee agreed to continue the work on biological methods criteria and to establish an EWG chaired by Chile and Mexico to:

- use the General Criteria for the Selection of Methods of Analysis included in the Procedural Manual and other related Procedural Manual reference documents for the validation of methods of analysis to assess methods, whose measurement basis of a substance are determined by the response of living organisms or living systems,
- determine which criteria would not apply and propose some other criteria that might be necessary for biological methods, which are currently endorsed by Codex.

EWG DISCUSSON

12. This EWG performed its functions on the platform http://forum.codex-alimentarius.net/, as recommended by the CCMAS Secretariat. A total of 34 users signed up to the platform, however, only comments from 3 delegations were received (Canada, Thailand and Kazakhstan), perhaps due to the difficulty to use the new platform. Unfortunately, it means a low representation of the opinion of delegates interested in the subject. The list of participants is included in Appendix II.

13. An initial document was presented to the EWG, where two examples of biological methods listed in the CX 234 were selected, these were chosen to represent biological methods that use living organisms such as AOAC 959.08 and methods that use microscopic organisms such as AOAC 992.07.

14. Each method was evaluated considering first the "General Criteria for the Selection of Methods of Analysis" and then the "guidelines for the establishment of numerical criteria", it was intended to look for practical evidence of the application of both criteria recognized by the Codex, this comparison was based on the information published in scientific journals and the information provided by EWG.

15. Finally, the EWG searched in other international references for the criteria that could be applied for the acceptance of biological methods, to subsequently investigate other numerical values in international guidelines such as the AOAC, to compare the available information with these criteria once again.

16. The conclusions resulted from the specific review of each one of the methods are available in Appendix I.

17. In general, it can be observed that biological methods meet certain criteria established in Codex, not only in situations associated to biological methods, but also to chemical methods that not necessarily meet strictly the criteria established by Codex. In such situations, it has been evaluated on a case-by-case basis and have been classified as Type II or III.

18. It is important to point out that when many biological methods were validated, the current criteria were not available, so it does not exist, or at least this EWG, could not count on that evidence, information necessary to verify compliance with all current criteria.

CONCLUSION

19. The performance criteria established in the Procedural Manual were established with the approach of approving chemical methods. However, some criteria can be applied for the adoption and classification of biological methods.

20. There are criteria that can be used by Codex for the adoption and classification of biological methods. For example: AOAC INTERNATIONAL Methods Committee Guidelines for Validation of Biological Threat Agent Methods and/or Procedures, AOAC Recommended Guidelines for Stakeholder Panel on Infant Formula and Adult Nutritionals (SPIFAN) Single-Laboratory Validation.

21. In the work carried out by this working group, it was evident that the scientific evidence used to support the adoption and classification of the methods listed in CXS 234 is not available. During the discussion of the WG, different scientific publications were reviewed but it is not known if those were the ones used by CCMAS at the time or if other references were consulted. Therefore, the Working Group invites the CCMAS to discuss a procedure to store or safeguard or track the scientific information that served to make decisions.

22. Methods included in international standards were necessarily evaluated and compared against certain criteria which were in force at the time of their adoption. And that there must have been evidence that the methods were is fit for the purpose.

23. Information consulted during the work of this EWG, allows us to conclude that the interlaboratory studies or the validation studies were developed before the approval of the current criteria and, therefore, do not fully comply with them.

RECOMMENDATIONS

24. If it is considered that the methods adopted by international standardization bodies, such as the AOAC or the ISO, have specific criteria for the adoption of the methods then, CCMAS should clarify what mechanism or procedure should be followed in order to distinguish if a method complies or not with the criteria accepted by Codex.

25. CCMAS must clarify if, for the adoption of the methods, it is necessary that the current criteria or criteria established at the time the method were developed, are met.

26. In case CCMAS determines that the current criteria are those that must be considered for the acceptance of the methods, then a critical analysis should be carried out to evaluate if the currently accepted methods fully comply with the current criteria.

27. In case CCMAS determines that the accepted methods can meet the criteria that were in force at the time of their adoption, then a procedure that allows to identify specifically, which are the criteria that were met at the time of the adoption of methods, should be available.

28. The exercise carried out by the EWG has also permitted to find a lack of information on the performance of the methods and CCMAS could need scientific evidence and clear records, specifying why it has been decided to adopt a certain method and its classification. Perhaps the scheme made in Annex I of this document could serve as an example of how to document decisions on adoption, ratification and typification of methods in the CCMAS.

29. The Committee is invited to consider:

- a procedure to save or protect or track the scientific information to make decisions regarding new methods listed in CXS 234 1999

- Regarding biological methodS, to discuss a way to proceed, using the current criteria on a case-by-case basis; or to develop specific criteria for biological methods

OBJECTIVE

To use the General Criteria for the Selection of Methods of Analysis included in the Procedural Manual and other related Procedural Manual referenced documents for the validation of methods of analysis to assess methods in which potency of a substance is measured by the response of living organisms or living systems, to determine which criteria would not apply and propose some other criteria that might be necessary for biological methods which are currently endorsed by Codex.

APPENDIX I

DOCUMENT REVIEWED AND DISCUSSED BY THE ELECTRONIC WORKING GROUP

A) INTRODUCTION

As was discussed by the Committee, many currently used microbiological methods to quantify vitamins may be replaced by HPLC methods, a list of proposals were sent to commodity committees for their consideration. There are still some biological methods considered useful for the quantification of vitamin B12, folates and pantothenic acid in foods. For the biological methods still listed in the CXS 234, it is relevant to have an adequate discussion that allows clarity on the correct application of the existing criteria for the adoption of biological methods.

During the Committee some delegates were of the opinion that the criteria for adoption of methods described in the Procedural Manual apply as found in biological methods. While the conclusions of the previous version of the EWG indicated that the parameters and their values were applied are different from those established in the procedural manual.

B) DISCUSSION

The difference in principles of biological and chemical methods is that the former are based on the response of a living organism, whereas the latter are based exclusively on an instrumental response. This aspect causes discrepancies in relation to the numerical criteria that are established by Codex with the objective of ratification of the methods.

Currently table 1 is the one used by the CCMAS for the acceptance and evaluation of the methods for its classification and acceptance:

Table 1: Guidelines for establishing numeric values for the criteria:

Applicability:	The method has to be applicable for the specified provision, specified commodity and the specified level(s) (maximum and/or minimum) (ML). The minimum applicable range of the method depends on the specified level (ML) to be assessed, and can either be expressed in terms of the reproducibility standard deviation (s_R) or in terms of LOD and LOQ.
Minimum applicable range:	For ML ≥ 0.1 mg/kg, [ML - 3 s_R , ML + 3 s_R] For ML < 0.1 mg/kg, [ML - 2 s_R , ML + 2 s_R] s_R[12] = standard deviation of reproducibility
Limit of Detection (LOD):	For ML ≥ 0.1 mg/kg, LOD ≤ ML · 1/10 For ML < 0.1 mg/kg, LOD ≤ ML · 1/5
Limit of Quantification (LOQ):	For ML ≥ 0.1 mg/kg, LOQ ≤ ML · 1/5 For ML < 0.1 mg/kg, LOQ ≤ ML · 2/5

Precision:	For ML ≥ 0.1 mg/kg, HorRat value ≤ 2 For ML < 0.1 mg/kg, the RSD_{TR} < 22%. RSD_R[13] = relative standard deviation of reproducibility. RSD_R ≤ 2. $PRSD_R$			
Recovery (R):	**Concentration**	**Ratio**	**Unit**	**Recovery (%)**
	100	1	100% (100 g/100g)	98 – 102
	≥10	10^{-1}	≥ 10% (10 g/100g)	98 – 102
	≥1	10^{-2}	≥ 1% (1 g/100g)	97 – 103
	≥0.1	10^{-3}	≥ 0.1% (1 mg/g)	95 – 105
	0.01	10^{-4}	100 mg/kg	90 – 107
	0.001	10^{-5}	10 mg/kg	80 – 110
	0.0001	10^{-6}	1 mg/kg	80 – 110
	0.00001	10^{-7}	100 µg/kg	80 – 110
	0.000001	10^{-8}	10 µg/kg	60 – 115
	0.0000001	10^{-9}	1 µg/kg	40 – 120
Trueness	Other guidelines are available for expected recovery ranges in specific areas of analysis. In cases where recoveries have been shown to be a function of the matrix other specified requirements may be applied. For the evaluation of trueness preferably certified reference material should be used.			

As stated in the *Guidelines on Analytical Terminology* (CXG 72-2009), the definition of LOD and LOQ "provides a basis for taking into account exceptions to simple case that is described, i.e. (non-normal distributions and heteroscedasticity (e.g. "counting" (Poisson) processes as those used for real time PCR). This exception can be translated into methods that are based on the growth of micro-organisms that also follow a Poisson distribution or that are based on the lethality of a population of organisms or an individual and that does not necessarily fulfill a normal distribution.

[1] ***CXG 72-2009***

Considering the work in the previous EWG and the agreements of the last session, we consider it convenient to review with some practical examples the applicability of the criteria established in the Manual of Procedures for biological methods.

Based on the method tables reported in CX/MAS 17/38/5, it is proposed to individually review the following methods.

Food	Provision	Method	Principle	Type
Bivalve molluscs	Paralytic Shellfish Poison	AOAC 959.08	Mouse Bioassay	IV
Special Foods	Pantothenic acid/	AOAC 992.07	Assay microbiological	II

The criteria established by the manual of procedures and other references will then be analyzed to define which criteria apply to biological methods and to establish the numerical values with which those methods should comply.

B.1. AOAC Method 959.08:

Food	Provision	Method	Principle	Type
Bivalve molluscs	Paralytic Shellfish Poison	AOAC 959.08	Mouse Bioassay	IV

B.1.1. Evaluation of compliance with the **"General Criteria for the Selection of Methods of Analysis"** according to the Manual of Procedures, Section II Elaboration of standards and related texts.

General Criteria	Verification	Comment
Official analysis methods developed by international organizations dealing with a food or group of foods	meets the requirement	OMA- Method
Selectivity	meets the requirement	LEDOUX and HALL: JOURNAL OF AOAC INTERNATIONAL VOL. 83, NO. 2, 2000.
accuracy	meets the requirement	Ibídem
Precision; Repeatability / in-laboratory (in the same laboratory), Interlaboratory reproducibility (in the same laboratory and in other laboratories)	meets the requirement	Ibídem
LOQ	meets the requirement	Ibídem
Sensitivity	No date	Ibídem
Practicality and applicability under normal laboratory conditions	meets the requirement	1) Ibídem VAN DE RIET ET AL.: JOURNAL OF AOAC INTERNATIONAL VOL. 92, NO. 6, 2009
Usual use	meets the	Ibídem

	requirement	
Concerning CODEX	meets the requirement	CODEX STAN 292-2008
Application to various food groups	Does not apply	Is only for Bivalve molluscs

B.1.2. Criterion approach. Establishment of numerical values relative to the criteria and comparison with validation studies

Parameter	**Codex Numerical values**	**LEDOUX and HALL: JOURNAL OF AOAC INTERNATIONAL VOL. 83, NO. 2, 2000.**	**Comment**
Applicability:	Analyte: Group of saxitoxins (STX). Disposition: Bivalve molluscs. ML: ≤0.8 milligrams (2HCl) of STX Eq/kg		
Lower level of the minimum application range:	0.42 - 1.18 mg/kg	0.524 mg/kg[5]	does not meet requirement
LOD:	0.08 mg/kg	not determined	No date
LOQ:	0.16 mg/kg	0.34 mg/kg in mussel y 0.41 mg/kg in clam[6] 0.1692 mg/Kg[7]	meet requirement
Precision :	16 %	1.528 mg/kg RSDr 9.78 RSDR 13.12 334.7 mg/kg RSDr 9.83 RSDR 39.57[8]	meet requirement
Recovery:	60-115% according to the procedures manual (50-130% according to CODEX STAN 292-2008)	1.528 mg/kg 35.1% 334.7 mg/kg 46.5%[9]	does not meet requirement
CRM:	Compliance with certified reference materials	Factor conversion	meet requirement

[5] LEDOUX and HALL: JOURNAL OF AOAC INTERNATIONAL VOL. 83, NO. 2, 2000.
[6] Van de Riet et al., Journal of AOAC International Vol.94 No.4 2011. pp. 1154-1176
[7] Validation protocol for PSP and Lipophilic Toxins Biological Methods, Community reference Laboratory for Marine Biotoxins. Agencia Español de Seguridad Alimentaria, Van de Riet et al., Journal of AOAC International Vol.94 No.4 2011. pp. 1154-1176
[8] LEDOUX and HALL: JOURNAL OF AOAC INTERNATIONAL VOL. 83, NO. 2, 2000.
[9] LEDOUX and HALL: JOURNAL OF AOAC INTERNATIONAL VOL. 83, NO. 2, 2000.

B.1.3. Appendix I: AOAC INTERNATIONAL Methods Committee Guidelines for Validation of Biological Threat Agent Methods and/or Procedures[10]

	Collaborative study	LEDOUX and HALL: JOURNAL OF AOAC INTERNATIONAL VOL. 83, NO. 2, 2000.	Comment
Number of Collaborators	8 to 12	8	meet requirement
Contamination levels	4	3	does not meet requirement
Number of test portions	2	2	meet requirement
RSDr	32	1.528 mg/kg RSDr 9.78 334.7 mg/kg RSDr 9.83	meet requirement
RSDR	32	1.528 mg/kg RSDR 13.12 334.7 mg/kg RSDR 39.57	meet requirement
Recovery	80-110% Recovery	1.528 mg/kg 35.1% 334.7 mg/kg 46.5%	does not meet requirement

B.1.4. Comments on the method

Based on the results presented in the previous tables we can propose that the bioassay method can meet the "General Criteria for the Selection of Methods of Analysis", since all the proposed determinations can be measured in a bioassay, in fact the method has a validation study in which it can be confirmed that it has met the established criteria. Thus, the method is suitably eligible to be considered within CODEX standards, however according to the manual procedure, for classification as Type II or III it is necessary to identify criteria and quantitative values that allow classification. So using the working instruction for the Application of criteria approach was considered to calculate the numerical values relative to the criteria, by reviewing the available evidence. It can be concluded that the study does not evaluate parameters such as the working range or limit of detection, this may be due to the nature of the method. The AOAC recognizes that there is a difference between chemical or instrumental methods and biological methods, and establishes in its guidelines specific criteria to evaluate the performance of the methods, these are: RSDr, RSDR, BIAS, suggesting that, Lower level of minimum application, LOD, LOQ, are not required for this type of determination.

When comparing the results of the collaborative study against the parameters of the AOAC guidelines, it can be observed that these were partially fulfilled at the time of the study, even the same interlaboratory study article concludes that "The recovery, using a spiked oyster issue matrix, was very good (> 90%) for LC analyzes, but the results based on the bioassay for the low and moderate PSP levels were poor (35 and 47%, respectively). While the results were good overall, the authors noted that several AOAC protocols needed to be revised or clarified "and although the 2001 report of the Committee on Natural Toxins and Food Allergens reports some research. The revised publications, on comparative studies, demonstrate the same trend of sub-quantification at a ratio of 2X, of the STX concentration, by the bioassay method.

The inherent lack of specificity in older methods has resulted in the development of more precise instrumental based methods. In contrast to biological methods, chemical methods are often capable of targeting specific/individual analytes.

However, in this sense, the maximum limit allowed is not established individually for each of the toxins corresponding to the saxitoxin group, but in equivalent units for saxitoxin. That is, from the point of view of innocuousness, the individual determination of each toxin is not relevant. Therefore, the requirement of selectivity for each toxin would not have to be met.

[10] AOAC International Methods Committee. AOAC INTERNATIONAL Methods Committee guidelines for validation of biological threat agent methods and/or procedures. J AOAC Int. 2011 Jul-Aug;94(4):1359-81.

In sum it can be said that the AOAC Method 959.08, meets the general criteria for the establishment of performance criteria and therefore can be considered for use as type IV methods. According to the procedures manual other references can be used to establish the criteria with which they must comply, the AOAC has set specific criteria for compliance with biological methods. It should be noted that the performance criteria established for these types of methods that use animals to measure a biological risk are only ML, precision, accuracy, bias and other parameters such as LOD, LOQ and linear range are not applicable to the nature of the method.

B.2. Method AOAC 992.07:

Food	Provision	Method	Principle	Type
Special Foods	Pantothenic acid/	AOAC992.07	Assay microbiological	II

B.2.1. Evaluation of compliance with the "General Criteria for the Selection of Methods of Analysis" according to the Manual of Procedures, Section II Elaboration of standards and related texts.

General criteria	Verification	Comment
Official analysis methods developed by international organizations dealing with a food or group of foods	meets the requirement	OMA- Method AOAC 992.07
Selectivity	No report	OMA AOAC 992.07
accuracy	No report	OMA AOAC 992.07
Precision; Repeatability / in-laboratory (in the same laboratory),Interlaboratory reproducibility (in the same laboratory and in other laboratories)	meets the requirement	OMA AOAC 992.07
LOQ	meets the requirement	OMA AOAC 992.07
Sensitivity	No date	
Practicality and applicability under normal laboratory conditions	meets the requirement	OMA AOAC 992.07
Usual use	meets the requirement	OMA AOAC 992.07
Concerning CODEX	meets the requirement	OMA AOAC 992.07

Application to various food groups	Does not apply	----------

B.2.2. Criterion approach. Establishment of numerical values relative to the criteria and comparison with validation studies

Parameter	**CODEX Numerical Values**	**CODEX Numerical Values date of proficiency testing**	**AOAC 992.07**
Aplicability	Considering the value of the standard. Analyzed: Ac. Pantothenic Disposition: Infant formulas ML: 68.2 mg / kg	Analyzed: Ac. Pantothenic Disposition: Infant formulas 4.80 mg / L (mean value of interlaboratory study)	meets the requirement
Range of aplication:	60.02 - 76.38 mg/kg	does not apply	Does not report
LOD:	6.82 mg/kg	does not apply	Does not report
LOQ:	13.64 mg/kg	does not apply	0.008 mg/L
Precision :	HORRRAT <= 2 RSDR= 6%	HORRRAT <= 2 RSDR= 6%	RSDr= 4.59%(meets) RSDR=10.23 % (not meets)
Recovery:	90-107 %	80-110%	Does not report
CRM:	1849a	does not apply	Does not report

B.2.3. Application of Appendix L criteria: AOAC Recommended Guidelines for Stakeholder Panel on Infant Formula and Adult Nutritionals (SPIFAN) Single-Laboratory Validation.

Linearity	6 level
LOD	LOD = blank mean + 3 standard deviations
LOQ	LOQ = blank mean + 10 standard deviations (concentration of blank to be <10% of the estimated LOQ)
Specificity	adequate evaluation
Precision	SRM 1849a
Accuracy	SRM 1849a (68.2mg/kg) Or samples spike recovery 50 to 150%

B.2.4. Comments on the method

The Method does not provide validation information or no information was found.

There is an interlaboratory study the results are reported in the Methods but the publication is not available.

References were found that indicate specific criteria for the type of product, so it might be advisable that the method meets only those criteria.

Although the Codex and AOAC criteria are the same, it is noted that sufficient evidence was not found to demonstrate that the method meets all the established criteria, so that its classification as type II may not be correct, researchers have summarized the methods for vitamins and in the particular case of pantothenic, conclude that so far there is no more appropriate method.

The available validation studies are incomplete compared to the current criteria so there seems to be a lack of clear information at the time of typing of the methods.

This discrepancy in decision-making in CCMAS may be due to a lack of documented information which should be made available to Committee members for future review. In any case, a case-by-case analysis may be appropriate in order to carry out a correct classification, but the scientific evidence supporting the decisions must be mentioned in the report of the Commission or in any case provided during the physical meeting for approval of the methods and sampling plans. The scientific information that supports the decision-making should remain available for future revisions.

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- Guidelines on analytical terminology (CAC/GL 72-2009)

APPENDIX II

8 List of EWG participants

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