1 April 2015

European Union Comments

CODEX COMMITTEE ON PESTICIDE RESIDUES

47th Session

Beijing, China, 13 – 18 April 2015

AGENDA ITEM 8

PROPOSED DRAFT GUIDELINES ON PERFORMANCE CRITERIA SPECIFIC FOR METHODS OF ANALYSIS FOR DETERMINATION OF PESTICIDES RESIDUES IN FOOD

(CX/PR 15/47/10)

European Union Competence
European Union Vote

The European Union (EU) would like to thank the electronic working group chaired by the United States and co-chaired by China for the preparation of the document on 'Proposed draft Guidelines on performance criteria specific for methods of analysis for determination of pesticides residues in food.'

However, the EU noticed with great disappointment that in the document CX/PR 15/47/10 the EU contribution to the eWG of the EU and some of its Member States has not been taken on board and no reasoning for this decision was given. The EU would have appreciated better communication and greater transparency in the workings of the eWG.

EU would like to make the general comment that throughout the document it should be clarified which criteria apply to initial method validation and which ones to routine analysis.

Furthermore, the EU wishes to provide the following specific comments:

Page	Paragraph	Comment	Rationale
Page #	Paragraph #	Added text is indicated in bold and underlined, removed text is indicated in strikethrough text.	
5	12	**For example, t**o minimally estimate	This procedure applies mainly to qualitative methods for

Page	Paragraph	Comment	Rationale
		rates of false positives and negatives during method validation, analyze ≥20 each of diverse matrix blanks (not from the same source) and spiked matrices at the analyte reporting level (e.g., 50% of the MRL).	quantitative methods other approaches can be performed as checking the slope and intercept of the linear regression of recoveries obtained during the validation at various levels
5	13	"The procedures described here relate to calibration studies in **initial** validation, which are ~~necessarily~~ more ~~involved~~ **extensive** than calibration**s** undertaken during routine analysis.	Add the word "initial". It is important to distinguish between initial and on-going (extended) validation.
5	15	Linearity can be tested by examination of a plot of residuals produced by linear regression of the responses on the concentrations in an appropriate calibration set **(For multi-level calibration, individual residuals must not derive more than 20%)**. Any curved pattern …	It is necessary to propose a criterion for the evaluation of linearity of the calibration curve especially for low levels and to estimate the necessity to use or not, weighted linear or weighted quadratic functions.
5	16	Replicate measurements are needed to provide an estimate of pure error if there is no independent estimate. In the absence of specific guidance, the following should apply **for the initial method validation** (for univariate linear calibration) :	A clear distinction should be made between initial validation of the method and the daily quality control checks as regards calibration, recoveries, etc... In the document it is not clear whether the performance parameters to be characterised and defined for analytical methods should be studied routinely or only during the validation of the method. A good example of this can be found in paragraph 16 as regards calibration (the calibration standards should be run at least in duplicate, and preferably triplicate or more, in a random order). This should refer to the initial validation, as doing so routinely would be impractical.
5	16	There should be **preferably** ~~five~~ **three** or more calibration standards.	
5	16	Change wording of the following bullet-point: "the range should encompass **the entire concentration range likely to be encountered (e.g.** LOQ–150%) ~~concentration likely to be encountered~~; and "	In many cases it is reasonable or at least not critical to choose a narrower range. For example in validation experiments where recoveries are expected to be in the range between 80 and 110 % it is enough to calibrate in the range between, e.g. 60 and 120% of the theoretical value. However, in market control any concentration below the CXL can occur. It is better to give as an example 'LOQ-150%' because establishing 0-150% means that 0 concentration (blank) has to be evaluated and considered and in general this is not the case. Logically LOQ is always evaluated.

Page	Paragraph	Comment	Rationale
6	18	Change wording of the following sentence: "The test should be done in a way that provides **approximately** the same final dilution as produced in the normal procedure, and the range of additions should encompass the same range as the procedure-defined calibration validation."	There is a practicability issue here. During spiking of blank extracts the volume and with it the matrix concentration will change automatically. If the dilution factor is not dramatic (<15%) the differences in matrix effects compared to an undiluted extracts will be insignificant. Where internal standards are used such volume differences can be easily compensated. Differences in matrix effects between matrices of the same type may be even more pronounced in some cases. .
6	18	If desired, total extractability can be measured by comparing the **own method** ~~MRM~~ with the official method provided by the registrants.	This also applies to any method, also single residue methods
6	19	Bias is typically determined by comparing the response of the method to a reference material **(internal or external)** with a known value assigned to the material	If a reference material is not available, it is necessary to produce one. A minimum of 10 replicates in reproducibility conditions is necessary.
6	20	Recovery refers to the proportion of analyte remaining at the point of the final determination, following its addition (usually to a blank sample) ~~immediately~~ prior to extraction, generally expressed as a percentage. Routine recovery refers to the determination(s) performed with the analysis of each batch of samples.	It makes no sense to extract residue immediately after spiking. A delay is needed to let the solvent evaporate at minimum. Various delays can be applied, ranging from 30 min. to overnight (in the case of food of animal origin).

Page	Paragraph	Comment	Rationale
7	26	The common accepted definition of LOQ is the concentration at which signal to noise (S/N) ratio is 10. ~~This reflects 95% confidence (19 out of 20 times) that an analyte at that concentration will be determined~~. The LOQ is typically only an estimate because determination of the precise LOQ takes many analyses of spiked samples and matrix blanks to accurately determine signal/noise, which is typically a fruitless exercise because the LOQ changes from day-to-day depending on the state of the instrument. Some validation guidelines require that the LOQ be verified to meet method performance criteria via spiking experiments at the LOQ, but a better term for use of this concept is lowest validated level (LSVL). Furthermore, quantification of analytes should not be made below the lowest calibrated level (LCL) in the same analytical sequence. The Signal to noise (S/N) ratio at the LCL must be ≥10 (conc. ≥ LOQ), which can be set as a system suitability check required for each analytical sequence. A quality control matrix spike can also be included in each sequence to verify that the reporting limit (RL, an action level that should be equal or greater than the LCL and the LSVL) is achieved in the analysis ~~(an action level is typically greater than the LCL)~~. In essence, the point of the validation is not to determine the LOQ, but to demonstrate that the lowest reported concentration meeting the need for the analysis will be equal to or greater than the LOQ.	The 95% confidence criterion seems to come from the LOD definition which refers to identification. In quantification S/N>10 may typically lead to acceptable precision (RSD) but will not guarantee acceptable accuracy (bias). There is many other factors having an influence in this. LSVL is preferred tp LCL as validation can be successful (meeting the criteria) or unsuccessful. In this case must be successful
8	34	…may be based on ~~microbiological growth inhibition, immunoassays, or chromogenic responses~~ **mass spectrometric techniques (in full scan)** which may not unambiguously identify a compound. ~~Mass spectrometric techniques also are used for screening purposes.~~	Microbial growth inhibition, immunoassays or chromogenic responses are not relevant for pesticide residues.
9	39	**During initial validation,** a minimum of 5 replicates **(in conditions of reproducibility)** is required (to check the recovery and precision) at the targeted **LSVL** ~~LOQ~~ or reporting limit	To be in agreement with chapter 26

Page	Paragraph	Comment	Rationale
		of the method, and at least one additional higher level, for example, 2-10x the targeted LOQ or the MRL.	
9	39	However, a more accurate method should be used, if practicable. Within-laboratory reproducibility, which may be determined from on-going quality control data in routine analyses, should be ≤ 20%, excluding any contribution due to sample heterogeneity. Acceptable mean recoveries range from 70-120% with a RSD ≤20%. **Individual recoveries in routine multi-residue analysis of 60-140% can be accepted,**	Criteria should be added for on-going quality control in routine analysis (as opposed to the initial method validation where the mean recoveries should be between 70-120%).
9	40	The trueness of a method may be **ideally** determined by analysis of a certified reference material **or a comparative test material**, by comparison of **own** results with **the respective assigned values**. **Alternatively accuracy can be demonstrated by comparing results obtained using the own method with results** ~~those~~ obtained using another method for which the performance parameters have previously been rigorously established (typically, a collaboratively studied method), or by determination of the recovery of analyte fortified into known blank sample material.	For better clarity of the sentence. In addition to the analysis of CRMs, which are often not available the participation in proficiency tests is also a good means of assessing the accuracy of a laboratory.
9	40	"~~At relatively high concentrations, analytical recoveries are expected to approach one 100%.~~ At lower concentrations, particularly with methods involving extensive extraction, isolation, and concentration steps, recoveries may be lower **due to losses in each step**. "	It is true that certain types of losses, e.g. those related to interactions with surfaces and sometimes oxidations will decrease in proportional (percentage) terms. This however will not apply to losses related to partitioning between phases which are mainly related to the types of solvents involved their volumes and the polarity of the analyte.

Page	Paragraph	Comment	Rationale
10	41	However, a more accurate method should be used, if practicable. ~~If available and affordable, participation in a proficiency testing program should be done.~~ Recovery corrections should be made consistent with the guidance provided by the CAC/GL 37-2001.	Move in chapter 40, usually, participation to proficiency test is used to estimate the ability of a laboratory to perform a method (most of all by the estimation of the trueness).
10	42	When appropriate, the detection system may be calibrated using standard solutions in a blank matrix ~~similar to that of the sample to be analyzed~~ (matrix-matched standards) which **is able to** compensate for matrix effects and **has** ~~if present,~~ acceptable interference **if present**.	Standard solutions sometimes are prepared in a matrix extract which is not similar to that of the sample to be analysed, but which is able to compensate for matrix effects and has acceptable interference. The reason for this is that often a similar matrix is not available or not feasible due to the presence of different matrices in the same sequence. For example, for GC analysis other matrices than the similar matrix will be able to satisfactorily compensate for matrix effects.
10	42	To achieve accurate results using a standard addition approach, it is essential to assure a linear response in the concentration range investigated. **Another alternative solution for compensating matrix effects can be the dilution of the sample, provided that the sensitivity of the detector is sufficiently high.**	The dilution of extract is usually the simplest approach to compensate matrix effect if the sensitivity of the detector is sufficiently high
10	43	The development of a separate confirmatory method is not generally needed when the original method is based on mass spectrometry or another highly specific technique. By far, gross error (mistakes) is the greatest source of misidentifications in MS-based methods. For this reason, all regulatory enforcement actions require confirmation of the result via re-extraction of a replicate test portion of	This document is a guideline with performance criteria for analytical methods. Economic considerations are not to be taken into account.

Page	Paragraph	Comment	Rationale
		the original sample and re-analysis, ideally using different chemistries of sample preparation and/or analysis. ~~Millions of dollars, international relations, and personal/business reputations may be at stake in regulatory determinations, and the laboratory must be sure of that all reports of residue violations are correct and validated.~~	
10	45	c.) the ratios of peak areas for each ion transition should match the ratios of the standard(s) within specified criteria. ~~Options include using ±10% absolute for one transition or ±20% absolute for two or more transitions, or~~ following the criteria stated in Table 2;	Leaving the choice between using ±10% absolute for one transition or ±20% absolute for two or more transitions, **or** following the criteria stated in Table 2 is confusing. It is better to only refer to table 2.
11	45	d.) reagent and matrix blanks must be shown to be free of carry-over, contamination, and/or interferences above an appreciable level **(<30% LSVL);**	A criterion needs to be specified.
11	46	Table 1 : remove TOF in unit mass resolution Quadrupole, ion trap, ~~time-of-flight (TOF).~~	Time of flight is a high resolution detector
12	51	Retention time data base should be adjusted for the current conditions. ~~In tolerance intervals of 1.5 to 3% of the absolute retention time may be applied for capillary GC depending on the peak shape. For confirmation of the retention time, the absolute tolerance intervals will increase at higher retention time.~~ The tolerance interval should be less than 0.2 minutes or 0.2% relative retention time (RRT). ~~For higher retention times, 6 seconds is a suitable interval~~	The RT threshold given here does not match with the threshold given in paragraphs 45 and 49.
14	Appendix I	Matrix-matched standards: standard solutions prepared in a matrix extract ~~similar to that of the sample to be analyzed~~ which **is able to** compensate for matrix effects **and has acceptable interference**, if present.	Standard solutions sometimes are prepared in a matrix extract which is not similar to that of the sample to be analysed, but which is able to compensate for matrix effects and has acceptable interference. The reason for this is that often a similar matrix is not available or not feasible due to analyses of different matrix in the same run. For example, for GC analysis other matrices than the similar matrix will be able to satisfactorily compensate for matrix effects.