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CODEX ALIMENTARIUS COMMISSION

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World Health Organization

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON PESTICIDE RESIDUES

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PROPOSED DRAFT GUIDELINES ON PERFORMANCE CRITERIA SPECIFIC FOR METHODS OF ANALYSIS FOR THE DETERMINATION OF PESTICIDE RESIDUES

(Prepared by the Electronic Working Group led by the United States of America)

(AT STEP 4)

Codex Members and Observers wishing to submit comments at **Step 3** on this document (**see Appendix I**), including possible implications for their economic interests, should do so in conformity with the *Uniform Procedure for the Elaboration of Codex Standards and Related Texts* (Codex Alimentarius Commission Procedural Manual) before **20 April 2014**. Comments should be directed:

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BACKGROUND

1. The 45th Session of the Committee on Pesticides (CCPR) (May 2013) agreed to start new work on guidance on performance criteria specific for methods of analysis for determination of pesticide residues. In taking this decision, the Committee agreed to establish an electronic working group chaired by the United States and co-chaired by China working in English only.[1]

2. The 36th Session of the Codex Alimentarius Commission (CAC) (July 2013) approved the proposal as presented by the CCPR.[2]

3. The document is based on two rounds of comments received by the Chairpersons from members of the EWG. The list of participants of the EWG is presented in Appendix II.

[1] REP13/PR, para. 140 and Appendix XII.
[2] REP13/CAC, Appendix VI.

APPENDIX I

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

DEFINITIONS

Analyte: The chemical substance sought or determined in a sample.

Analyte protectant: Compounds that strongly interact with active sites in the gas chromatographic (GC) system, thus decreasing degradation, adsorption, or both of coinjected analytes.

Confirmatory method: A method that provides complementary information in agreement with a previous result. Ideally, a different subsample is analyzed with a method involving a different chemical mechanism than in the first analysis, and one of the methods meets analyte identification criteria with an acceptable degree of certainty at the level of interest

Determination: Quantitative result of a method, but which has not yet met identification or confirmation criteria.

False positive: A result wrongly indicating that the analyte concentration is present or exceeds a specified value

False negative: A result wrongly indicating that the analyte concentration is not present or does not exceed a specified value.

Identification: Process of unambiguously determining the chemical identity of a pesticide or metabolite in experimental or analytical situations.

Incurred residue: Residue identified in a commodity resulting from specific use of a pesticide or from consumption by an animal or environmental contamination in the field, as opposed to residues identified from laboratory fortification of samples.

Interferent: any chemical or physical phenomenon that can interfere with or disrupt a reaction or process

Limit of detection (LOD): The true net concentration or amount of the analyte in the material to be analyzed which will lead, with probability (1-β), to the conclusion that the concentration or amount of the analyte in the analyzed material is larger than that in the blank material.

Limit of quantification (LOQ): A method performance characteristic generally expressed in terms of the signal or measurement (true) value that will produce estimates having a specified relative standard deviation (RSD), commonly 10% (or 6%).

Matrix: The material or component sampled for pesticide residue studies.

Matrix blank: Sample material containing no detectable concentration of the analytes of interest.

Matrix-matched standards: standard solutions prepared in a matrix extract similar to that of the sample to be analysed which compensate for matrix effects and acceptable interference, if present.

Maximum Residue Level (MRL): Maximum concentration of a residue that is legally permitted or recognised as acceptable in, or on, a food, agricultural commodity or animal feedstuff as set by Codex or a national regulatory authority. The term tolerance used in some countries is, in most instances, synonymous with MRL (Normally expressed as mg/kg fresh weight).

Multiresidue method (MRM): Analytical method which measures a number of pesticide residues simultaneously.

Quantitative method: A method capable of producing analyte concentration (determinative) results with trueness and precision that comply with established criteria.

Relative Standard Deviation (RSD): It is the standard deviation, divided by the absolute value of the arithmetic mean, expressed in percentage. It refers to the precision of the method. Considering a single laboratory, the precision is expressed in terms of repeatability (RSD_r) and reproducibility (RSD_{wR}) within the laboratory.

Relative Standard Deviation of repeatability (RSD_r): The precision of measurement of an analyte, obtained using the same method on the same sample(s) in a single laboratory over a short period of time, during which differences in the materials and equipment used and/or the analysts involved will not occur.

Relative Standard Deviation of within laboratory reproducibility (RSD_{wR}): The precision of measurement of an analyte obtained using the same method on different samples, in a single laboratory, over a long period of time, during which differences in the materials and equipment used and the analysts involved will occur.

Repeatability: For an analytical method, the closeness of agreement between results of measurements on identical test material subject to the following conditions: same analyst, same instrumentation, same location, same conditions of use, repetition over a short period of time.

Reproducibility: For an analytical method, the closeness of agreement between results of measurements on identical test material where individual measurements are carried under changing conditions such as: analyst, instrumentation, location, conditions of use, time.

Screening detection Limit (SDL): The screening detection limit of a qualitative screening method is the lowest concentration for which it has been demonstrated that a certain analyte can be detected (not necessarily meeting unequivocal identification criteria) in at least 95% of the samples (i.e. a false negative rate of 5% is accepted).

Screening method: A method that meets predetermined criteria to detect the presence of an analyte or class of analytes at or above the minimum concentration of interest.

Selectivity: Selectivity refers to the extent to which the method can be used to determine particular analytes in mixtures or matrices without interferences from other components of similar behaviour. Some regulatory authorities use the term specificity to refer to selectivity.

Sensitivity: Quotient of the change in the indication of a measuring system and the corresponding change in the value of the quantity being measured.

Specificity: The ability of the detector to provide signals that effectively identify the analyte. (GC-MS with EI is a fairly nonselective determination system capable of high specificity. High resolution mass MS and MS^n can be both highly selective and highly specific).

SCOPE

1. The purpose of this guidance document is to describe the performance criteria of methods to analyze pesticide residues in foods and feeds. It addresses characteristics/parameters that analytical methods should have in order to provide internationally acceptable confidence in the method to produce accurate results to evaluate pesticide residues for either domestic programmes or in international trade.

2. This document is applicable to single, multiresidue, or multiclass multiresidue methods (MRMs) to analyse target compounds in food commodities, including parent pesticide residues and/or their metabolites and degradates in food commodities, as per the definition of residue.

3. In this document, a MRM is considered to be a method which can determine three or more analytes in the same chemical class or in more than one class of pesticide. This guidance covers qualitative (screening, identification, confirmation) and quantitative analyses, each having different method performance requirements. It should be noted that a validated MRM may be used to determine analytes where performance characteristics for quantitative analysis have been fully validated, but should be limited to qualitative purposes for analytes lacking full validation.

PRINCIPLES FOR THE SELECTION AND VALIDATION OF METHODS

IDENTIFICATION OF METHODS REQUIREMENTS

Method scope

4. The intended purpose of the method is usually defined in a statement of *scope* which defines the analytes (residues), the matrices and the concentration range to which the method applies. It also states whether the method is intended for screening, quantitation, identification, and/or confirmation of analytes.

5. The MRL is expressed in terms of the "definition of residue", which may include the parent compound, a major metabolite, a sum of parent and/or metabolites, or a reaction product formed from the residues during analysis. Residue analytical methods should be able to measure all components of the residue definition.

6. Selection of methods is discussed in CAC/GL 40-1993, Guidelines on Good Laboratory Practice in Pesticide Residue Analysis.

Implementing other Codex Alimentarius Commission Guidelines

7. The Codex Alimentarius Commission has issued a guideline for laboratories involved in the import/export testing of foods which recommends that such laboratories should:

(a) Use internal quality control procedures, such as those described in the "Harmonised Guidelines for Internal Quality Control in Analytical Chemistry laboratories";

(b) Participate in appropriate proficiency testing schemes for food analysis which confirm to the requirement laid out in "the International Harmonized Protocol for Proficiency Testing of (Chemical) Analytical Laboratories"

(c) Comply with the general criteria for testing laboratories provided in ISO/IEC Guide 17025:2005 "General requirements for the competence of calibration and testing laboratories"; and

(d) Whenever available, use methods which have been validated according to principles provided by the Codex Alimentarius Commission.

8. The methods should be used within the internationally accepted, approved, and recognized laboratory Quality Management System, which is consistent with the principles in the document for quality assessment (QA) and quality control (QC) referenced above. The on-going performance must be monitored through the Quality Management System in place in the laboratory.

Method Validation and Fitness for Purpose

9. The process of method validation is intended to demonstrate that a method is *fit-for-purpose*. This means that in the hands of a properly trained analyst using the specified equipment and materials, and following the procedures described in the method, reliable and consistent results can be obtained within specified statistical limits for the analysis of a sample. The validation should specify the analyte (identity and concentration), account for the matrix effect, and provide a statistical characterization of the recovery results. When the method protocol is followed, using suitable analytical standards, results within the established performance limits should be obtained on the same or equivalent sample material by a trained analyst in any experienced residue control laboratory.

SUMMARY OF PERFORMANCE PARAMETERS TO BE CHARACTERISED AND DEFINED FOR ANALYTICAL METHODS

10. The general requirements for the individual performance characteristics for a method are summarize below from IUPAC's Harmonized guidelines for single-laboratory validation of methods of analysis.

A. APPLICABILITY

After validation, the documentation should provide, in addition to any performance specification, the following information:

- identity of the analyte, including speciation where appropriate (e.g., "total arsenic");
- concentration range covered by the validation (e.g., "0–50 ppm");
- specification of the range of matrices of the test material covered by the validation (e.g., "seafood");
- protocol, describing the equipment, reagents, procedure (including permissible variation in specified instructions, e.g., "heat at 100 ± 5°C for 30 ± 5 min"), calibration and quality procedures, and any special safety precautions required; and
- intended application and critical uncertainty requirements (e.g., "The analysis of food for screening purposes (Standard uncertainty u(c) of the result c should be less than 0.1 × c.").

B. SELECTIVITY

Ideally, selectivity should be evaluated for any important interferent likely to be present. It is particularly important to check interferents that are likely, on principal chemicals, to respond to the test. For example, colorimetric tests for ammonia might reasonably be expected to respond to primary aliphatic amines. It may be impracticable to consider or test every potential interferent; where that is the case, it is recommended that the likely worst cases are checked. As a general principle, selectivity should be sufficiently good for any interferences to be ignored. In many types of analysis, selectivity is essentially a qualitative assessment based on the significance or otherwise of suitable tests for interferents.

C. CALIBRATION AND LINEARITY

With the exception of gross errors in preparation of calibration materials, calibration errors are usually (but not always) a minor component of the total uncertainty budget, and can usually be safely subsumed into other categories. For example, random errors resulting from calibration are part of the run bias, which is assessed as a whole, while systematic errors from that source may appear as laboratory bias, likewise assessed as a whole. Nevertheless, there are some characteristics of calibration that are useful to know at the outset of method validation, because they affect the strategy for the optimal development of the procedure. In this class are such questions as whether the calibration function plausibly (a) is linear, (b) passes through the origin, and (c) is unaffected by the matrix of the test material. The procedures described here relate to calibration studies in validation, which are necessarily more exacting than calibration undertaken during routine analysis. For example, once it is established at validation that a calibration function is linear and passes through the origin, a much simpler calibration strategy can be used for routine use (for example, a two-point repeated design). Errors from this simpler calibration strategy will normally be subsumed into higher-level errors for validation purposes.

Linearity and intercept

Linearity can be tested informally by examination of a plot of residuals produced by linear regression of the responses on the concentrations in an appropriate calibration set. Any curved pattern suggests lack of fit due to a nonlinear calibration function. Despite its current widespread use as an indication of quality of fit, the correlation coefficient is misleading and inappropriate as a test for linearity and should not be used.

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 univariate linear calibration):

- there should be six or more calibration standards;
- the calibration standards should be evenly spaced over the concentration range of interest;
- the range should encompass 0–150% or 50–150% of the concentration likely to be encountered, depending on which of these is the more suitable; and
- the calibration standards should be run at least in duplicate, and preferably triplicate or more, in a random order.

Test for general matrix effect

A test for general matrix effect can be made by applying the method of analyte additions (also called "standard additions") to a test solution derived from a typical test material. The test should be done in a way that provides the same final dilution as the normal procedure produces, and the range of additions should encompass the same range as the procedure-defined calibration validation. If the calibration is linear, the slopes of the usual calibration function and the analyte additions plot can be compared for significant difference. A lack of significance means that there is no detectable general matrix effect. If the calibration is not linear, a more complex method is needed for a significance test, but a visual comparison at equal concentrations will usually suffice. A lack of significance in this test will often mean that the matrix variation effect (Section I) will also be absent.

D. TRUENESS AND RECOVERY

Trueness is the closeness of agreement between a test result and the accepted reference value of the property being measured. Trueness is stated quantitatively in terms of "bias", with smaller bias indicating greater trueness. Bias is typically determined by comparing the response of the method to a reference material with the known value assigned to the material. Significance testing is recommended. Where the uncertainty in the reference value is not negligible, evaluation of the results should consider the reference material uncertainty as well as the statistical variability.

E. PRECISION

Precision is the closeness of agreement between independent test results obtained under stipulated conditions. It is usually specified in terms of standard deviation or relative standard deviation. The distinction between precision and bias is fundamental, but depends on the level at which the analytical system is viewed. Thus, from the viewpoint of a single determination, any deviation affecting the calibration for the run would be seen as a bias. From the point of view of the analyst reviewing a year's work, the run bias will be different every day and will act like a random variable with an associated precision. The stipulated conditions for the estimation of precision take account of this change in viewpoint.

For single-laboratory validation, two sets of conditions are relevant: (a) precision under repeatability conditions, and (b) precision under run-to-run conditions. It is important that the precision values are representative of likely test conditions. First, the variation in conditions among the runs must represent what would normally happen in the laboratory under routine use of the method. For instance, variations in reagent batches, analysts, and instruments should be representative. Second, the test material used should be typical, in terms of matrix and (ideally) the state of comminution, of the materials likely to be encountered in routine application.

Precision very often varies with analyte concentration. Typical assumptions are (i) that there is no change in precision with analyte level, or (ii) that the standard deviation is proportional to, or linearly dependent on, analyte level. In both cases, the assumption needs to be checked if the analyte level is expected to vary substantially (that is, by more than about 30% from its central value).

Precision data may be obtained for a wide variety of different sets of conditions in addition to the minimum of repeatability and between-run conditions indicated here, and it may be appropriate to acquire additional information. For example, it may be useful to the assessment of results, or for improving the measurement, to have an indication of separate operator and run effects, between or within-day effects or the precision attainable using one or several instruments. A range of different designs and statistical analysis techniques is available, and careful experimental design is strongly recommended in all such studies.

F. RANGE

The validated range is the interval of analyte concentration within which the method can be regarded as validated. It is important to realize that this range is not necessarily identical to the useful range of the calibration. While the calibration may cover a wide concentration range, the remainder of the validation (and usually much more important part in terms of uncertainty) will cover a more restricted range. In practice, most methods will be validated at only one or two levels of concentration. The validated range may be taken as a reasonable extrapolation from these points on the concentration scale.

G. DETECTION LIMIT (LOD)

In broad terms, the LOD is the smallest amount or concentration of analyte in the test sample that can be reliably distinguished from zero. For analytical systems where the validation range does not include or approach it, the detection limit does not need to be part of a validation.

Despite the apparent simplicity of the idea, the whole subject of the detection limit is beset with problems outlined below:

- There are several possible conceptual approaches to the subject, each providing a somewhat different definition of the limit. Attempts to clarify the issue seem ever more confusing.
- Although each of these approaches depends of an estimate of precision at or near zero concentration, it is not clear whether this should be taken as implying repeatability conditions or some other condition for the estimation.
- Unless an inordinate amount of data is collected, estimates of detection limit will be subject to quite large random variation.
- Estimates of detection limit are often biased on the low side owing to operational factors.
- Statistical inferences relating to the detection limit depend on the assumption of normality, which is at least questionable at low concentrations.

H. LIMIT OF DETERMINATION OR LIMIT OF QUANTIFICATION (LOQ)

It is sometimes useful to state a concentration below which the analytical method cannot operate with an acceptable precision. Sometimes that precision is arbitrarily defined as 10% RSD, sometimes the limit is equally arbitrarily taken as a fixed multiple (typically 2) of the detection limit. Hence, the use of this type of limit in validation is not recommended here.

It is preferable to try to express the uncertainty of measurement as a function of concentration and compare that function with a criterion of fitness for purpose agreed between the laboratory and the client or end-user of the data.

I. SENSITIVITY

The sensitivity of a method is the gradient of the calibration function. As this is usually arbitrary, depending on instrumental settings, it is not useful in validation. (It may be useful in quality assurance procedures, however, to test whether an instrument is performing to a consistent and satisfactory standard.)

J. RUGGEDNESS

The ruggedness of an analytical method is the resistance to change in the results produced by an analytical method when minor deviations are made from the experimental conditions described in the procedure. The limits for experimental parameters should be prescribed in the method protocol (although this has not always been done in the past), and such permissible deviations, separately or in any combination, should produce no meaningful change in the results produced. (A “meaningful change” here would imply that the method could not operate within the agreed limits of uncertainty defining fitness for purpose.) The aspects of the method that are likely to affect results should be identified, and their influence on method performance evaluated by using ruggedness tests.

Examples of the factors that a ruggedness test could address are: changes in the instrument, operator, or brand of reagent; concentration of a reagent; pH of a solution; temperature of a reaction; time allowed for completion of a process, etc.

K. FITNESS FOR PURPOSE

Fitness for purpose is the extent to which the performance of a method matches the criteria, agreed between the analyst and the end-user of the data that describe the end-user’s needs. For instance, the errors in data should not be of a magnitude that would give rise to incorrect decisions more often than a defined small probability, but they should not be so small that the end-user is involved in unnecessary expenditure. Fitness-for-purpose criteria could be based on some of the characteristics described here, but ultimately will be expressed in terms of acceptable combined uncertainty.

I. Matrix variation

Matrix variation is, in many sectors, one of the most important but least acknowledged sources of error in analytical measurements. When we define the analytical system to be validated by specifying, among other things, the matrix of the test material, there may be scope for considerable variation within the defined class. To cite an extreme example, a sample of the class “soil” could be composed of clay, sand, chalk, laterite (mainly Fe_2O_3 and Al_2O_3), peat, etc., or of mixtures of these. It is easy to imagine that each of these types would contribute a unique matrix effect on an analytical method such as atomic absorption spectrometry. If we have no information about the type of soils we are analyzing, there will be an extra uncertainty in the results because of this variable matrix effect.

Matrix variation uncertainties need to be quantified separately, because they are not taken into account elsewhere in the process of validation. The information is acquired by collecting a representative set of the matrices likely to be encountered within the defined class, all with analyte concentrations in the appropriate range. The material are analyzed according to the protocol, and the bias in the results estimated. Unless the test materials are CRMs, the bias estimate will usually have to be undertaken by means of spiking and recovery estimation. The uncertainty is estimated by the standard deviation of the biases.

M. MEASUREMENT UNCERTAINTY

The formal approach to measurement uncertainty estimation calculates a measurement uncertainty estimate from an equation, or mathematical model. The procedures described as method validation are designed to ensure that the equation used to estimate the result, with due allowance for random errors of all kinds, is a valid expression embodying all recognized and significant effects upon the result. Guidelines on estimation of uncertainty of results are provided in CAC/GL 59-2006

PERFORMANCE CHARACTERISTICS OF METHODS

PERFORMANCE CHARACTERISTICS OF SCREENING METHODS

11. Screening methods are usually either qualitative or semi-quantitative in nature, with the objective being to discriminate samples which contain no detectable residues above a threshold value ("negatives") from those which may contain residues above that value ("potentially positives"). The validation strategy therefore focuses on establishing a threshold concentration above which results are "potentially positive", determining a statistically based rate for both "false positive" and "false negative" results, testing for interferences and establishing appropriate conditions of use. Screening methods should be checked for their selectivity and sensitivity. They can be based on test kits and their selectivity may be increased when a detection system is used after chromatographic or other separation techniques. Another approach is to use screening methods that involve automated Mass Spectrometry-based detection systems, which are very selective. These methods offer laboratories a cost-effective means to extend their analytical scope to analytes which potentially have a low probability of being present in the samples. Analytes that occur more frequently should continue to be sought and measured using validated quantitative multiresidue methods.

12. The Selectivity of screening methods should be adequate and must be able to distinguish the presence of the target compound, or group of compounds, from other substances which may be present in the sample material. It is normally not as great as that of a quantitative method. Screening methods often take advantage of a structural feature common to a group or class of compounds and may be based on microbiological growth inhibition, immunoassays, or chromogenic responses which may not unambiguously identify a compound. Mass spectrometric techniques also are used for screening purposes. The selectivity of a screening method may be increased when it is used as a detection system after chromatographic or other separation technique.

13. The validation of a screening method based on a screening detection limit (SDL) can be focused on detectability. For each commodity group, a basic validation should involve analysis of at least 20 samples spiked at the estimated SDL. The samples selected should represent multiple commodity categories from the commodity group, with a minimum of two different samples for each commodity category and should be representative for the intended scope of the laboratory. Additional validation data can be collected from on-going AQC-data and method performance verification during routine analysis. The SDL of the qualitative screening method is the lowest level at which an analyte has been detected (not necessarily meeting the MS-identification criteria) in at least 95% of the samples (i.e. an acceptable false-negative rate of 5%).

PERFORMANCE CHARACTERISTICS OF QUANTITATIVE METHODS

14. Selectivity is of particular importance in defining the performance characteristics of quantitative methods used in regulatory control programmes for pesticide residues in foods. The method needs to provide a signal response which is free from interferences from other analytes and matrix compounds which may be present in a sample or sample extract. Chromatographic analyses based on peaks which are not fully resolved provide less reliable quantitative results. Use of element-specific detectors or different detection wavelengths or mass-selective detectors which are better able to distinguish a particular compound or structure, combined with chromatographic separation, improves the selectivity of quantitative methods.

15. The requirement to recover a range of different pesticide residues in one extraction increases the potential for compromised selectivity in MRMs compared to single analyte methods. Using less selective extraction and clean-up procedures is likely to result in greater co-extracted matrix material in the final extract. The nature and quantities of such co-extracted material can vary markedly depending on the history of the individual sample. Particular care is therefore required when setting criteria for the precision and trueness of MRMs to ensure that quantification will not be affected by interference from other compounds present in the sample matrix.

16. In addition to the selectivity of a method, the ability of the method to provide a quantitative result which is reliable, i.e. accuracy must be demonstrated. This consists of two factors:

(a) The closeness of the result to the true or accepted value for the concentration of analyte present in the sample material, i.e. trueness (bias) of the result and

(b) The ability of the method to provide consistent results on replicate determinations, expressed in terms of precision (repeatability and reproducibility).

17. Acceptability criteria for a quantitative analytical method should be demonstrated at both initial and extended validation stages, as being capable of providing acceptable mean recovery values at each spiking level. A minimum of 5 replicates is required (to check the recovery and precision) at the targeted LOQ or reporting limit of the method, and at least one other higher level, for example, 2-10x the targeted LOQ or the MRL. Where the residue definition includes two or more analytes, then wherever possible, the method should be validated for all analytes included in the residue definition. Acceptable mean recoveries and associated repeatability are presented in Table 1). The method-LOQ is the lowest spike level of the validation meeting these method performance acceptability criteria. In certain cases and typically with multiresidue methods, recoveries outside this range may be accepted. Exceptionally, where recovery is low but consistent (i.e. demonstrating good precision) and the basis for this is well established (e.g. due to analyte distribution in a partitioning step), a mean recovery below 70% may be acceptable. However, a more accurate method should be used, if practicable. Within-laboratory reproducibility (RSD_{wR}), which may be determined from on-going quality control data in routine analyses, should be ≤ 30%, excluding any contribution due to sample heterogeneity.

Table 1: Mean recovery and precision criteria for plant animal matrices

Concentration level	Range of mean recovery (%)	Precision, RSD (%)
> 1 µg/kg ≤ 0.01 mg/kg	60 - 120	30
> 0.01 mg/kg ≤ 0.1 mg/kg	70 - 120	20
> 0.1 mg/kg ≤ 1.0 mg/kg	70 - 110	15
> 1 mg/kg	70 - 110	10

18. The accuracy of a method may be determined by analysis of a certified reference material, by comparison of results with 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. The latter determination of accuracy as recovery is frequently used in validation of methods for pesticide residues in foods, as both certified reference materials and methods validated by an inter-laboratory trial are often not available. The accuracy of a measurement is closely related to random error (repeatability error or within-lab reproducibility error), systematic error (analytical method bias) and analyte recovery (measured as percent recovery). Recovery should be assessed over concentrations which cover the analytical range of the method. In interpreting recoveries, it is necessary to recognize that analyte added to a sample may not behave in the same manner as the same biologically incurred analyte (pesticide residue). In many situations, the amount of an incurred residue that is extracted (the yield or recovered fraction) is less than the total incurred residues present. This may be due to losses during extraction, intra-cellular binding of residues, the presence of conjugates, or other factors that are not fully represented by recovery experiments conducted with analyte-fortified blank matrices. At relatively high concentrations, analytical recoveries are expected to approach one hundred percent. At lower concentrations, particularly with methods involving extensive extraction, isolation, and concentration steps, recoveries may be lower. In general, residues data do not have to be adjusted for recovery when the mean recovery is within the range of 70-120%. Exceptionally, where recovery is low but consistent (i.e. demonstrating good precision) and the basis for this is well established (e.g. due to analyte distribution in a partitioning step), a mean recovery below 70% may be acceptable. However, a more accurate method should be used, if practicable. If residues data are adjusted for recovery, then this must be stated.

19. Recovery corrections should be made consistent with the guidance provided by the Codex Alimentarius Commission. It is of over-riding importance that all data, when reported, should (a) be clearly identified as to whether or not a recovery correction has been applied and (b) if a recovery correction has been applied, the amount of the correction and the method by which it was derived should be included with the report. This will promote direct comparability of data sets. Correction functions should be established on the basis of appropriate statistical considerations, documented, archived and available to the client.

20. Quantitative methods are usually based on a comparison of the response from an analyte in a sample with the response from standards of the analyte in solution or in a matrix at known concentrations. In method development and validation, the calibration curve should first be determined to assess the detector response to standards over the range of concentrations of analytical interest. Possible matrix enhancement or suppression effects of sample co-extractives, on the chromatography system or detection system response should be addressed both in Gas Chromatography (GC) and Liquid Chromatography (LC) based methods. When appropriate, the detection system may be calibrated using standard solutions in a blank matrix similar to that of the sample to be analysed (matrix-matched standards) which compensate for matrix effects and acceptable interference, if present. An alternative practical approach to compensate for matrix effects in GC-analyses is the use of analyte protectants that are added to both the sample extracts and the calibration solutions in order to equalise the response of pesticides in solvent calibrants and sample extracts. When no suitable blank commodity is available for the preparation of the matrix-matched standards, the most effective way to compensate for matrix effects is the use of standard addition or use of isotopically labelled internal standards. The standard addition approach may compensate for matrix effects and also recovery of the analytical procedure but does not overcome chromatographic interferences. Using a standard addiction approach, it is essential to assure a linear response in the concentration range investigated for achieving accurate results.

PERFORMANCE CHARACTERISTICS OF METHODS FOR ANALYTE IDENTIFICATION

21. 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. On a case-by-case basis, additional confirmation may be necessary, for example when the first method is an immunoassay or when selective detectors, which offer only limited specificity, are coupled with GC or LC techniques as their use, even in combination with different polarity columns, does not provide unambiguous identification.

22. Selectivity is the primary consideration for methods of identification**.** The method should be sufficiently selective to provide unambiguous identification. Mass spectrometry coupled to a chromatographic separation method is a very powerful combination for identification of an analyte in the sample extract. These are often the techniques on which confirmatory methods are based. It simultaneously provides retention time, ion/charge ratios and relative abundance (intensity) data.

23. The following chromatography-MS/MS identification criteria must be met for regulatory purposes: 1.) the retention time of the detected analyte peak must be within 0.1 min of the contemporaneously analyzed analyte reference standard peak; 2.) the different ion transitions for the analyte should co-elute with similar peak shapes; 3.) the ratios of peak areas for each ion transition must match the ratios of the reference standard(s) within ±10% absolute for one transition or ±20% absolute for two transitions; 4.) reagent and matrix blanks must be shown to be free of carry-over, contamination, and/or interferences above an appreciable level; 5.) signal/noise ratios for measured peaks must be >3; 6.) the signal must exceed the threshold intensity level as compared to the signal of a suitable reference standard or control encompassing the level of interest; and 7.) the ion transitions chosen for identification purposes should make chemical/structural sense.

24. Methods based on high resolution mass spectrometry are considered to give a higher reliability through more precise measurement of mass than can be obtained using low resolution mass spectrometry techniques. Different types and models of mass spectrometric detectors provide different degrees of selectivity, which relates to the confidence in identification. The requirements for identification are given in Table 2. They should be regarded as guidance criteria for identification, not as absolute criteria to prove presence or absence of a compound.

Table 2: Identification requirements for different types of mass spectrometers

MS mode	Single MS (unit mass resolution)	Single MS (high resolution/high mass accuracy)	MS/MS
Typical systems (examples)	Quadrupole, ion trap, time-of-flight (TOF)	TOF, Orbitrap, FTMS, magnetic sector	Triple quadrupole ion trap, hybride MS (e.g. Q-TOF, Q-trap)
Acquisition	Full scan, Limited m/z range, Selected ion monitoring (SIM)	Full scan, Limited m/z range, Selected ion monitoring (SIM)	Selected/multiple reaction monitoring (SRM/MRM), full scan product-ion spectra
Requirements for identification	≥ 3 diagnostic ions, (preferably including quasi molecular ion)	≥ 2 diagnostic ions (preferably including the quasi molecular ion). Mass accuracy < 5 ppm. At least one fragment ion.	≥ 2 product ions

25. The relative abundances (intensities) or ratios of selective ions (full-scan MS or SIM) or product ions (MS/MS), expressed as a ratio relative to the most intense (product) ion, should correspond to those of the calibration standard at comparable concentrations and measured under the same conditions. Matrix-matched calibration solutions may need to be used. Table 3 below indicates the recommended maximum tolerances for ion ratios. The tolerances given in Table 3 should not be taken as absolute limits and automated data interpretation based on the criteria without complementary interpretation by an experienced analyst is not recommended.

Table 3: Recommended maximum (default) tolerances for ion ratios using different MS techniques

Ion ratio (least/most intense ion)	Maximum tolerance (relative) for GC-EI-MS	Maximum tolerance (relative) for LC-MS^n, LC-MS, GC-MS^n, GC-CI-MS
0.50-1.00	± 10%	± 30%
0.20-0.50	± 15%	± 30%
0.10-0.20	± 20%	± 30%
<0.10	± 50%	± 30%

26. Additional confidence is provided with the use of high resolution mass spectrometers (or detection using mass spectrometers with high resolving power, typically > 20,000 FWHM) which offer more precise identification of the mass and may be used to predict the elemental composition of each fragment. In addition, at least one ion ratio must also be measured to eliminate the potential for fragments of the same mass arising from isobaric compounds of similar structure.

27 The minimum acceptable retention time for the analyte(s) under examination should be at least twice the retention time corresponding to the void volume of the column. The retention time of the analyte in the extract should correspond to that of the calibration standard (may need to be matrix-matched) with a tolerance of ±0.2 min, for both gas chromatography and liquid chromatography. Greater retention time deviations are acceptable where both retention time and peak shape of the analyte match with those of a suitable IL-IS, or evidence from validation studies is available.

PERFORMANCE CHARACTERISTICS OF CONFIRMATORY METHODS

28. For enforcement actions, confirmation that analytes are present in the samples must be made by a second analysis, and one of the confirmatory methods should involve analyte identification, typically using MS techniques. Moreover, the confirmatory methods should use independent approaches based on different chemical mechanisms, such as liquid and gas chromatography (LC and GC) separations. In some situations, confirmation by independent laboratories may be appropriate. Examples of analytical techniques which may be suitable to meet criteria for confirmatory analytical methods are summarized in Table 4.

29. Whenever chromatographic techniques are used in screening or confirmation, proper settings of the retention time windows is pivotal. Care should be taken that the instrument is adjusted correctly before starting the analysis; a system suitability test should be performed prior to each batch of analysis. Retention times data base should be adjusted for the current conditions. In phase 1, 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 1 sec for an RT less than 500 sec. For retention times between 500 and 5000 sec. an interval of 0.2% RRT is recommended. For higher retention times 6 sec. is a suitable interval. Additional guidance is given in CAC/GL 56-2005, Guidelines on the Use of Mass Spectrometry for Identification, Confirmation and Quantitative Determination of Residues.

Table 4: Examples of detection methods suitable for the confirmatory analysis of substances, as recommended by the Miskolc Consultation

Detection method	Criterion
LC or GC and Mass Spectrometry	If sufficient number of fragment ions are monitored
LC-DAD	If the UV spectrum is characteristic
LC – fluorescence	In combination with other techniques
2-D TLC – (spectrophotometry)	In combination with other techniques
GC-ECD, NPD, FPD	Only if combined with two or more separation techniques
Derivatisation	If it was not the first choice method
LC-immunogram	In combination with other techniques
LC-UV/VIS (single wavelength)	In combination with other techniques

Other chromatographic systems (applying stationary and/or mobile phases of different selectivity) or other techniques

References:

1	CAC/GL 64-1995	Protocol for the Design, Conduct and Interpretation of Method Performance Studies
2	CAC/GL 40-1993 and its revisions	Guidelines on Good Laboratory Practice in Pesticide Residue Analysis
3	CAC/GL 56-2005	Guidelines on the Use of Mass Spectrometry (MS) for Identification, Confirmation and Quantative Determination of Residues
4	CAC/GL 59-2006	Guidelines on Estimation of Uncertainty of Results
5	CAC/GL 72-2009	Guideline on Analytical Terminology
6	CAC/GL 49-2003	Harmonized IUPAC Guidelines for Single-Laboratory Validation of Methods of Analysis © 2002 IUPAC, Pure and Applied Chemistry 74, 835–855
7	CAC/GL 27-1997	Guidelines for the Assessment of the Competence of Testing Laboratories Involved in the Import and Export Control of Food
8	CAC/GL 65-1997	Harmonized Guidelines for Internal Quality Control in Analytical Chemistry Laboratories, *Pure & Appl. Chem.*, **67** (1995) 649-666
9	CAC/GL 71-2009	Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programme associated with the Use of Veterinary Drugs in Food Producing Animals
10	CAC/GL 37-2001	Harmonized IUPAC Guidelines for the use of Recovery Information in Analytical Measurement. Pure Appl. Chem., Vol. 71, pp. 337 – 348, 1999
11	SANCO/12571/2013	SANCO Analytical quality control and validation procedures for pesticide residues analysis in food and feed update of SANCO/12495/2011
12	ENV/JM/MOMO(2007)17	Guidance Document on Pesticide Residue Analytical Methods OECD Environment, Health and safety Publications, Series on Testing and Assessment, No. 72, Series on Pesticides No. 39
13	ENV/JM/MONO(2009)30	OECD Guidance Document on the Definition of Residue
14	SANCO/825/00 rev 8.0 (16/11/2010)	"Guidance document on pesticide residue analytical methods".
15	IUPAC Selectivity in Analytical Chemistry	Selectivity in analytical chemistry, International Union of Pure and Applied Chemistry Vol. 73 No. 8, pp. 1381-1386, 2001
16	IUPAC Glossary of Terms Relating to Pesticides	Glossary of Terms Relating to Pesticides. International Union of Pure and Applied Chemistry Vol. 68, No.5, pp. 1167-1193, 1996
17	ISO VIM	ISO International Vocabulary of Basic and General Terms in Metrology (VIM)
18	S.J. Lehotay et. al.	Identification and Confirmation of Chemical Residues in Food by Chromatography – Mass Spectrometry and Other Techniques. Trends in Analytical Chemistry Vol 27, No. 11, pp.1070-1090, 2008

APPENDIX II

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