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VALIDATION OF ANALYTICAL METHODS FOR FOOD CONTROL

A Report of a Joint FAO/IAEA Expert Consultation
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CONTENTS

ANNEX

1. INTRODUCTION

A Joint FAO/IAEA Expert Consultation on Validation of Analytical Methods for Food Control was held in Vienna, Austria, from 2 to 4 December 1997. The Consultation participants are listed in Annex 1. The Consultation was opened by Dr. James Dargie, Director, Joint FAO/IAEA Division, who welcomed the participants on behalf of the Directors-General of both FAO and IAEA.

In welcoming the participants, Dr. Dargie outlined the increased emphasis and importance of Codex activities and standards within the Joint FAO/IAEA Division, especially as they relate to international trade. Many of these standards involve chemical analysis of food products and such analyses must be conducted with appropriate and validated analytical methods. Up to the time of this Consultation, the validation requirements of a method used for Codex purposes have been rigourous and in some instances Codex Committees have requested extensive collaborative studies. There are, however, alternative validation procedures which this Consultation has been asked to consider. For a method to be accepted and used by national governments, the validated method must be both practical and suitable for use. Dr. Dargie underlined the importance of the Consultation in providing international guidance and recommendations in this area. He also stressed the importance of the Consultation in guiding future work within the recently established FAO/IAEA Training and Reference Centre for Food and Pesticide Control. He pointed out that the fundamental objective of this Centre was to assist member nations in implementing Codex standards to facilitate international trade in food and agricultural commodities and thereby assist sustainable food security.

The Consultation Secretary, Mr. Anthony Whitehead, added his welcome to the participants and reminded them that two points should be considered during their deliberations. First, it is important that recommendations made by the Consultation be based on sound science as a primary consideration. Mr. Whitehead pointed out that important decisions will be made based upon the Consultation recommendations, especially as regards the requirements for food quality and safety in the global food trading system. Those decisions must be based on proper science in order to accommodate risk analysis considerations.

Mr. Whitehead also asked the Consultation to consider the constraints and barriers faced by developing countries in applying method validation requirements that are not always practical for their needs. He stressed the importance of flexibility so as to provide alternatives for countries needing assistance in these matters.

Mr. Whitehead provided the participants with the basic objectives of the Consultation, which were:

- to review existing international methods validation schemes;
- to identify requirements for validation of methods in the analytical areas of veterinary drug and pesticide residues, food additives and environmental contaminants in food; and
- to recommend alternative approaches to methods validation which would be practical and cost effective, and which would consider time and human resource constraints.

The Consultation elected Dr. Dieter Arnold as Chairman and Dr. Jacques Boisseau as Vice Chairman. Dr. Richard Ellis was appointed as Rapporteur. In accepting the Chair, Dr. Arnold also stressed the importance of the Consultation and informed the participants that timely elaboration of Codex maximum residue limits (MRLs) for veterinary drug residues in food

requires validated analytical methods. Workable alternative validation procedures would assist in providing such methods. Dr. Arnold further noted that guidance on method validation was in fact needed by several Codex committees and was also vitally important for providing methods to determine compliance with food safety standards within the provisions of the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) and aiding in resolution of food safety disputes with the World Trade Organization.

2. BACKGROUND

There is a continuing need for reliable analytical methods for use in determining compliance with national regulations as well as international requirements in all areas of food quality and safety. The reliability of a method is determined by some form of a validation procedure. The Codex Alimentarius Commission (CAC), for example, requires that in order for a method of analysis to be included in a Codex commodity standard, certain method performance information should be available. This includes specificity, accuracy, precision (repeatability, reproducibility), limit of detection, sensitivity, applicability and practicability, as appropriate. This very often requires an extensive collaborative study be undertaken to obtain the necessary data. Methods which have successfully undergone this performance review testing have been considered to be validated for purposes of analyses under Codex commodity standards.

The ideal validated method is one that has progressed fully through a collaborative study in accordance with international harmonized protocols for the design, conduct and interpretation of method performance studies. This usually requires a study design involving a minimum of 5 test materials, the participation of 8 laboratories reporting valid data, and most often includes blind replicates or split levels to assess within-laboratory repeatability parameters.

It is not practical or necessary to require that all analytical methods used for food control purposes be assessed at the ideal level, especially methods for the determination of low-level contaminants in foods, such as veterinary drug and pesticide residues. Limiting factors for completing ideal multi-laboratory validation studies include high costs, lack of sufficient expert laboratories available and willing to participate in such studies, and overall time constraints.

A validated method for the analysis of veterinary drug residues in foods has been separately defined by the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) (1), as an analytical method which has been subjected to ruggedness testing and a multi-laboratory study for accuracy, precision and reproducibility. These performance factors facilitate development of inter-laboratory quality assurance documentation and provide consistency of results, on which an appropriate method of analysis for food control purposes can be established. Such a method would also include appropriate written procedures for sample selection and preparation as well as the final quantitation of the analyte being tested.

At the national level there are many methods available and used for routine food control analyses which have been selected on the basis of their performance characteristics. In many cases, however, these methods have not been subjected to inter-laboratory validation trials. An analytical method must be properly validated if it is to be used at the national level for enforcement purposes. Validated methods stand on their own merits in contested legal actions in national courts. This situation has been recognized by the Codex Committee on Methods of Analysis and Sampling (CCMAS), which has proposed to the CAC to commence a new work item using the concept of local or within-laboratory method validation based on international general guidelines.

Within this environment, the entire area of validation of analytical methods used in food control for Codex purposes has been discussed at length by the CCMAS, as well as the CCRVDF and the Codex Committee on Pesticide Residues (CCPR). All three Committees supported the holding of a consultation to provide expert advice and guidance in this area. The present Joint FAO/IAEA Consultation on Validation of Analytical Methods for Food Control was convened for that purpose.

The Consultation was asked to review present method validation criteria and approaches in the light of past experience, taking into account available resources. In doing this, the Consultation was to consider whether analytical methods for food control purposes could be validated under performance-based criteria using either inter-laboratory or intra-laboratory data combined with laboratory analytical quality assurance systems and/or other widely accepted analytical performance guidelines.

3. ANALYTICAL METHODS IN CODEX

The Role of Methods

The Consultation considered the importance of methods of analysis for the elaboration of Codex standards and their subsequent use in determining compliance to those standards. The operating premise of the Consultation was that methods should be transferable between laboratories to help ensure the uniform application of Codex standards. A method is considered to be transferable when it provides equivalent results, taking into account the method performance characteristics, when used in other competent laboratories. Proper validation of the method is inherent in transferability. Validated analytical methods should be included in Codex Standards in particular where they are necessary to determine the presence of potentially hazardous substances in foods, e.g., veterinary drug and pesticide residues as well as other contaminants in foods, which may exceed established limits. However, such methods of analysis should only be recommended if their reliability and performance has been recognized.

The Consultation reviewed the current role of validated analytical methods in the development of Codex Standards on the basis of relevant Codex Committee documents, including the Guidelines for the Acceptance Procedures for Codex Standards and the Guidelines for the Inclusion of Specific Provisions in Codex Standards and Related Texts, both described in the Procedural Manual of the Codex Alimentarius Commission (2).

Types of Methods

The CAC has elaborated Principles for the Establishment of Codex Methods of Analysis (3), which classify methods of analysis as: Type I, Defining Methods; Type II, Reference Methods; Type III Alternative Approved Methods; and Type IV, Tentative Methods. This classification was designed primarily for the Codex commodity committees. Most methods currently listed for pesticide and veterinary drug residues would qualify according to this classification as tentative methods, while only those which had been subject to a collaborative study as defined by internationally accepted harmonized protocols would meet the requirements for Type I, II or III methods.

For Codex Type I, II or III methods, statistical parameter estimates for reproducibility are generally obtained from a collaborative study. A typical study of a determinative method conducted in accordance with the internationally harmonized ISO/IUPAC/AOAC[1] protocol could require a minimum of up to five materials including blind replicates or split level samples, and eight participating laboratories (4).

The Codex Alimentarius classification of methods for residues of veterinary drugs in foods, is based on the intended use of the method, not directly on the validation status (5). A Level III method is defined as suitable for screening (usually semi-quantitative); a Level II method is a determinative method that provides a quantitative estimate of the residue concentration; while a Level I method is a confirmatory method that unambiguously identifies the analyte and which may also provide quantitative information. Included with the intended use are recommended performance criteria for accuracy, precision and recovery.

[1] International Organization for Standardization (ISO)/International Union for Pure and Applied Chemistry (IUPAC)/ AOAC International (AOAC)

Method Performance Criteria

The CAC has established the required information for all methods adopted by or referred to it (6). This includes, for each individual proposed method, information relating to specificity, accuracy, precision (repeatability, reproducibility), limit of detection, sensitivity, applicability and practicability, as appropriate. Other criteria may be selected as required. The Consultation noted that the CCRVDF had supplemented these criteria with two additional performance-based characteristics, limit of quantitation and systematic error.

The Consultation affirmed these method performance criteria, including those formulated by the CCRVDF, as being relevant and appropriate for methods of analysis for Codex purposes. Regarding the criterion concerning limit of detection, it was considered necessary that it be included in a validation study only where method performance indicates that the limit of quantitation approaches the Codex standard.

As noted above, the Consultation also affirmed that Codex methods should be transferable between laboratories. Therefore, when establishing Codex methods of analysis, preference should be given to analytical methods whose performance has been established in respect to the above criteria.

The Consultation noted that the CCMAS had agreed in principle to accept an alternative approach for evaluating analytical methods (7), whereby a defined set of selection criteria to which methods should comply is established, without specifically endorsing particular methods for adoption (the “criteria-based approach”). CCMAS believes that this approach gives greater flexibility than the present procedure. It also ensures that analysis methods may be used as soon as they become suitably validated and available.

The Consultation recognized that the minimum requirements concerning the information on precision as applied by CCRVDF when recommending methods for determining compliance with Codex MRLs were less stringent, requiring independent validation by a minimum of three analysts, preferably in three different laboratories (8). Validation of most of the proposed methods for determining residues of veterinary drugs in foods historically has demonstrated that a requirement for a full collaborative trial, while desirable, is impractical due to the complex nature of the matrices and the associated costs for performing such studies. In such circumstances, reliance has been placed primarily on the 3-analyst, 3-laboratory criteria, with the performance characteristics obtained from within-laboratory or between laboratories and certain quality assurance data. It is important, therefore, that this process is carried out in a manner consistent with the fitness for purpose of the methods. Whenever possible, however, methods recommended to date by the CCRVDF as suitable for routine monitoring to determine compliance with a MRL, have been subjected to a full collaborative study.

The Consultation was aware of the fact that the Joint FAO/WHO Expert Committee on Food Additives (JECFA) assesses the adequacy of analytical methods used in the conduct of pharmacokinetic and residue depletion studies when reviewing submissions supporting applications for MRLs of veterinary drugs. In the case of new drugs, such studies would normally be conducted under the provisions of Good Laboratory Practice (GLP). The results of the evaluation of such analytical methods are subsequently included in the JECFA reports, with a summary of the method principles and performance parameters, where appropriate.

The Consultation noted that procedures for identifying methods for Codex purposes differ among certain Codex committees. For example, the CCPR has whenever possible applied the following criteria for the selection of methods for inclusion in the Codex Alimentarius recommended methods of analysis (9):

- publication of methods in books, manuals or the open literature;
- availability of the results of a collaborative study or validation in a large number of laboratories;
- capability of determining more than one residue, i.e. multi-residue methods;
- applicability to the analysis at or below MRL levels, for as many different commodities as possible;
- applicability in official laboratories carrying out routine analyses.

The FAO/WHO Joint Meeting on Pesticide Residues (JMPR) which provides scientific advice to the CCPR, does not directly recommend analytical methods. However, in situations where field trials have revealed no detectable residues, the limit of determination of the test method used in the trial forms the basis for the estimation of an MRL set, "at or about the limit of determination".

The Codex Committee on Food Additives and Contaminants (CCFAC) considers the question of establishing maximum levels for food additives and chemical contaminants in foods. The Committee has, from time to time, identified additives for which there is a need to establish methods of analysis where the absence of such methods is considered as a potential trade problem. Methods judged suitable by CCFAC are proposed to CCMAS for endorsement and subsequent adoption by the Commission. The JECFA provides scientific advice to the CCFAC and, like the JMPR, does not directly recommend methods of analysis.

4. VALIDATION CRITERIA FOR METHOD PERFORMANCE

Introduction

As discussed previously, it is required that methods of analysis used for Codex purposes be subjected to a collaborative study carried out in conformity with internationally accepted guidelines. Alternative validation schemes using fewer laboratories and fewer samples for veterinary drug residue methods have been applied, however. The Consultation acknowledged that even the CCRVDF alternative (three analysts, preferably in three laboratories) has frequently not been met.

The Consultation agreed that the multi-laboratory model already adopted by the CAC is the preferred option for validation of methods of analysis. If a full collaborative study conducted according to internationally accepted guidelines cannot be conducted, the Consultation recognizes that the three-laboratory model (or equivalent) should be applied. In those cases where this less stringent model cannot be used, other validation protocols must be used. This can include a two laboratory "peer review" approach or internal validation within a single laboratory (see part 6 of this report). If a one or two laboratory approach is taken, the responsible organization should indicate their rationale in selecting the chosen validation scheme. This will permit users to evaluate the recommended methods accordingly.

Method Characteristics

The general criteria considered by the Consultation for the establishment of method performance characteristics and subsequent selection of chemical analytical methods are given below. With one exception (limit of quantitation), these criteria are the same as those used by the CAC (3). The Consultation made the following comments in describing the criteria.

Specificity - Details concerning specificity must relate at least to those substances which might be expected to give rise to an interfering signal when the measuring principle is used. In residue analysis, for example, they may include substances which give a response similar to the residue being measured. The details concerning specificity must quantitatively indicate the extent to which the method can distinguish between the analyte of interest and interfering substances under the experimental conditions. A check for random interferences should be performed by analysis of a set of representative blank samples.

Accuracy - Accuracy refers to the closeness of agreement between the true value of the analyte concentration and the mean result that is obtained by applying the experimental procedure a large number of times to a set of homogeneous samples. It is closely related to systematic error and analyte recovery. The accuracy requirements of methods will vary depending upon the planned use of the results. Generally, accuracy at or below the MRL or level of interest must be equal to or greater than the accuracy above the MRL or level of interest. The percent recovery of an analyte that is added to a blank test sample is a related measurement that compares the amount found by analysis to the amount added to the sample. 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 (veterinary drug residues, for example). At relatively high concentrations, analytical recoveries are expected to approach 100%. At lower concentrations and particularly with methods involving a number of steps including extraction, isolation, purification and concentration, recoveries are often lower. Regardless of what average recoveries are observed, recovery with low variability is desirable.

Precision - The precision of a method is the closeness of agreement between independent test results obtained from homogeneous test material analyzed under the stipulated conditions of use. Repeatability and reproducibility as defined in the Protocol for the Design, Conduct and Interpretation of Method Performance Studies (4) can best be estimated when the validation is carried out as a collaborative study. However, in the absence of a collaborative or other multi-laboratory study, the laboratory must obtain an estimate of the method's repeatability and within-laboratory reproducibility from data produced by that single laboratory. The precision of a method may also be estimated within a single laboratory using measurement reliability procedures as described in the ISO guide on the estimation of measurement uncertainty (10).

Limit of quantitation - The limit of quantitation is the smallest measured content above which a determination of the analyte is possible with a specified degree of accuracy and repeatability (within-laboratory reproducibility). In general, the limit of quantitation of a method is associated with its limit of detection. In practice the limit of detection need only be determined when the limit of quantitation of the method approaches the limit specified in the applicable standard, such as a maximum residue limit. The limit of detection is generally of lesser importance than the limit of quantitation because residue limits established by Codex, for example, are never zero.

Sensitivity - This is the change in the analytical response divided by the corresponding change in the concentration of a standard (calibration) curve, i.e. the slope of the analytical calibration curve. A method is said to be sensitive if a small change in concentration of the analyte causes a large change in the analytical measurement. Although the analytical response may vary with the magnitude of the analyte concentration, it is usually constant over a reasonable range of concentrations (11). In the ideal situation, the calibration curve becomes a straight line, expressing a direct linear relationship between analytical response and standard concentration.

Practicability and applicability under normal conditions - This refers to the ease with which a method may be applied by those skilled in analysis. Preference should be given to methods of analysis which are applicable to a broad range of matrices and analytes. It also may include application to multi-residue methods. The method should be assessed over the relevant range of concentration, taking as a minimum half the value of the specified limit and twice the specified limit.

Other criteria which may be selected as required - These may include ease of use, use of routine and versatile instruments, availability of reagents, etc.

5. ELABORATION OF ANALYTICAL METHODS FOR RESIDUES

Introduction

Analytical methods for residues of veterinary drugs and pesticides require technical considerations not specified in the principles adopted by the CAC for more general use. Therefore, analytical methods that are suitable for the identification and measurement of the target analytes at established MRLs are required. Methods elaborated by the alternative procedures noted in part 6 of this report should be proposed for use in residue programs for food control.

Method Guidance

The primary objective for the elaboration of a analytical method is to provide a procedure that is generally recognized as meeting established criteria so that the method may be widely accepted and used for determining compliance with MRLs. This primary objective does not exclude the use of an accepted Codex analytical method as a reference method in helping arbitration organizations resolve disputes between countries concerning food residue control problems affecting international trade. The Consultation firmly recognized that in potential disputes it is the preponderance of scientific data, not just the analytical method, that must be considered.

Codex analytical methods may also serve as a recognized analytical standard for the calibration and performance evaluation of other useful analytical methods. The availability of an operational standard for performance evaluation of analytical methods would provide countries and other users with valuable flexibility in the use of analytical methods for monitoring compliance with residue MRLs for foods. The use of a Codex analytical method as an operational performance standard for the assessment of the suitability of other methods of analysis for determining compliance with an MRL, requires the user to design and successfully execute appropriate experiments. This extension of recommended methods for food control purposes must be carried out within a quality assurance system that will provide the data necessary to demonstrate the comparative performance of the method with the Codex method for the intended new use.

While the provision of suitable, validated analytical methods is a necessary requirement for assuring compliance with MRLs, the method alone is not sufficient to assure creditable analytical measurements. In addition to using suitable methods, the user of the method must demonstrate that the method is operating under statistical control in the laboratory and that the user is able to perform the method to meet performance specifications as required by the analytical problem. This means that all methods should be applied in an environment having appropriate quality assurance procedures and performance evaluation checks.

The Consultation discussed the availability of suitable analytical methods for determining compliance of residues in tissues of so-called minor species with established MRLs. Often, the performance characteristics of a residue method have been determined only for major food animal or plant species. The Consultation concluded that if the metabolism and related pharmacokinetic data are similar in minor species to that in major species, only the demonstration of acceptable recovery of the analyte in minor species needs to be determined. If the recovery remains stable, there is no need to study the method’s performance any further. If the recovery is not stable, a full set of performance data should be determined.

Methods Accessibility

The elaboration of analytical methods useful for generating data for the estimation of MRLs also requires that a private or public sector interested party (e.g. a sponsor) take responsibility for the generation and provision of the necessary data. Without this interest and commitment, elaboration of analytical methods and MRLs would become very difficult.

It is important that all the recommended available data on analytical performance characteristics are submitted to JECFA or JMPR in the sponsor's dossier. In those cases where data are submitted to national registration authorities, it is important that these data be made available to JECFA and JMPR. This will greatly help to minimize discrepancies in the mutual interpretation of data and to facilitate international harmonization efforts.

6. ALTERNATIVE PROCEDURES FOR ESTIMATING PERFORMANCE CHARACTERISTICS

Introduction

The Consultation reviewed current procedures for assessing method validation criteria. It was noted that in general, it is required that before Codex methods are accepted, they are tested in inter-laboratory methods performance (collaborative) studies in order to obtain a reliable estimation of the performance characteristics of the method. Such studies should be designed, conducted and its results interpreted and reported in accordance with internationally recognized protocols or standards.

As noted above, the Consultation acknowledged that in recent years it has become evident that it is neither practical nor always possible to estimate the performance characteristics of methods for the analysis of residues of veterinary drugs or pesticides using internationally accepted protocols for inter-laboratory studies. The recently adopted increased requirements on internal and external laboratory quality control measures (12) adds an extra level of confidence to chemical measurements. This Consultation agreed that the increase in such confidence permits alternative approaches to method validation to be considered.

Alternative Procedures

The Consultation affirmed that the preferred validation procedure is a collaborative study carried out according to generally accepted international protocols. In those instances when for practical reasons that procedure is not feasible or suitable, a three or more laboratory validation protocol may be used as a second option. The third option would be a two laboratory validation protocol (e.g. similar to the AOAC International Peer Verified Method Protocol) and the final option would be a single laboratory validation protocol. With any of the alternative validation schemes, the Consultation strongly encourages that the validation work be conducted according to the five principles outlined below:

1. The laboratories carrying out the method validation operate under an appropriate, quality system based on internationally recognized principles.
2. The laboratories have in operation a periodic, independent, third party assessment mechanism of their quality system and validation work, carried out by, e.g. an accreditation agency, a GLP authority, or one or more collaborating laboratories. Alternatively, the laboratory carrying out the validation may submit the validation work for peer review to be assessed by an appropriate, professional organization. Such an independent assessment and review helps to ensure the transferability of the validated method from the originating laboratory to other laboratories.
3. The analytical method is assessed according to the criteria noted above, using the definitions that have been adopted by the Commission (3). In those instances where the CAC has not adopted a definition, the definitions given in part 4 of this report may be used.
4. The validation work should be carefully documented in a validation report in which it is unambiguously stated for which purposes (matrices and analyte levels) the method has been found to perform in a satisfactory manner.
5. Evidence of transferability.

The Consultation noted that those participants from developing countries found these alternative validation schemes, with the principles listed above, acceptable to their needs and their resources.

Codex Quality Requirements for Laboratories

The Consultation noted that the Codex Alimentarius Commission at its 22nd Session in June 1997 had adopted guidelines for the assessment of the competence of testing laboratories involved in the Import and Export Control of Foods (13). The guidelines (14) require that the laboratories:

- use internal quality control procedures which comply with the "Harmonised Guidelines for Internal Quality Control in Analytical Chemistry" (15);
- participate in proficiency testing schemes designed and conducted in accordance with the "International Harmonised Protocol for Proficiency Testing of (Chemical) Analytical Laboratories" (16); and
- become accredited according to ISO/IEC Guide 25 "General requirements for the competence of calibration and testing laboratories" (17).

In addition, the guidelines include that laboratories "...whenever available, use methods which have been validated according to the principles laid down by the Codex Alimentarius Commission".

The Consultation noted that many developing countries have appropriate quality assurance procedures in place in their regulatory laboratories and that their laboratory personnel are highly educated, motivated and trained. While all laboratories analyzing samples for food control purposes should adopt these new guidelines, laboratories in developing countries ought to be among the first.

The Consultation agreed that the decision of the CAC which established three new formal requirements for the quality management of certain analytical chemical control laboratories was a very important step, to focus not only on method validation requirements but to bring the entire analytical system to a higher level of quality standards. If comparable measures would be taken in all areas of chemical food analysis this would favourably change the environment in which chemical methods of analysis are currently being developed and validated and would thereby greatly facilitate the elaboration of valid methods including those used to monitor compliance with Codex Standards.

7. CONCLUSIONS

The Consultation **CONCLUDED** that:

- There is a continuing need for analytical methods to be used in determining compliance with international standards and the identification of appropriate and reliable methods is an integral part of decision making in a risk analysis framework.
- The preferred means to validate an analytical chemical method used to determine compliance with Codex limits is a full collaborative study using internationally accepted protocols and in which all the participating laboratories operate under internationally accepted principles of quality assurance. However, due to decreasing resources available for such studies at the national level and other factors including but not limited to, insufficient numbers of qualified laboratories to participate and increased costs, full collaborative studies are less frequently undertaken.
- Due to the above conditions, some Codex Committees have developed criteria which vary in their rigour for the identification of methods which can be recommended for determining compliance with Codex standards.
- Chemical analytical methods used in veterinary drug residue depletion studies in target animals constitute a potential source of suitable methods for determining compliance of tissue residues with established MRLs. In some situations these methods may have been used in several laboratories conducting depletion studies in the same analyte/tissue combination. Similar considerations may be available for pesticide residue methods. Often, however, the information on these analytical methods may not have been studied or processed any further for their suitability as regulatory methods.
- There should be analytical chemical methods available to governments for use in determining if veterinary drug and pesticide residues or traces of food contaminants comply with MRLs or other requirements. With regard to developing countries, participants from those countries noted that the criteria for method validation proposed by the Consultation are suitable for their needs.
- The purpose of use of analytical chemical methods, such as screening, quantitation and confirmation, is an issue to be decided by national food control authorities.

8. RECOMMENDATIONS

The Consultation **RECOMMENDS** that:

1. MRLs for pesticides and veterinary drug residues as well as Maximum Levels for contaminants in foods should be established with reference to analytical methods suitable for the monitoring of compliance with the respective MRL.
2. All methods used for determining compliance with international or other standards which have not been subjected to a full collaborative study should be subject to a form of independent review, which may include a multi-laboratory study involving a smaller number of laboratories, second laboratory verification, validation in a laboratory operating under GLP or validation in a laboratory which has been recognized under ISO/IEC Guide 25, or equivalent.
3. Appropriate Codex committees as well as national agencies who establish MRLs in food should select analytical methods on the basis of their suitability to determine compliance with those MRLs.
4. The evaluation of methods should form an integral part of the evaluation of substances carried out by the JECFA and JMPR. These expert committees should also establish procedures to evaluate and recommend methods for the analysis of residues, for consideration by the competent Codex Committees as Codex methods. In doing so, the expert committees would be guided by the established procedures and stated needs of the Codex committees.
5. Sponsors or other parties submitting data for evaluation and determination of an MRL, should provide an expert report on analytical methods that are used in studies (e.g. drug residue depletion) including their performance characteristics. This would enable a review of these methods for their suitability for determining compliance with recommended MRLs.
6. In those cases where collaborative studies or other inter-laboratory studies are impractical or impossible to carry out, evaluations of analytical methods could be done in one laboratory, provided that the validation work is conducted according to the five principles discussed in the body of this report. In brief, these principles are:
    - Laboratories carrying out the validation studies operate under a suitable quality system based upon internationally recognized principles;
    - Laboratories have in operation a third party review of the whole validation process (e.g. GLP registration, accreditation according to ISO/IEC Guide 25, or Peer Review);
    - Analytical methods are assessed in respect to the Codex general criteria for selection of methods of analysis (3), with emphasis on the assessment of the limit of quantitation rather than the limit of detection.
    - The validation work be carefully documented in an expert validation report in which it is unambiguously stated for which purposes (matrices and analyte levels) the method has been found to perform in a satisfactory manner; and
    - Evidence of transferability be provided for all methods intended for Codex use for food control purposes.
7. All analytical methods accepted for Codex purposes to determine compliance with MRLs, including performance characteristics data, should be made available by Codex to member countries.

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ANNEX

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