IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

WHO ILO UNEP

Environmental Health Criteria 240

Principles and Methods for the Risk Assessment of Chemicals in Food

Chapter 3
CHEMICAL CHARACTERIZATION, ANALYTICAL METHODS AND THE DEVELOPMENT OF SPECIFICATIONS

A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization

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Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.

Food and Agriculture Organization of the United Nations

World Health Organization

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO) and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

WHO Library Cataloguing-in-Publication Data

Principles and methods for the risk assessment of chemicals in food.

(Environmental health criteria ; 240)

1. Risk assessment. 2. Hazard assessment. 3. Exposure assessment. 4. Dose-response assessment. 5. Chemicals. 6. Food safety. 7. Food additives. 8. Contaminants. 9. Pesticide residues. 10. Veterinary drug residues. I.World Health Organization. II.Food and Agriculture Organization of the United Nations.

ISBN 978 92 4 157240 8 (NLM classification: WA 712)
ISSN 0250-863X

This document was technically and linguistically edited by Marla Sheffer, Ottawa, Canada.

Printed by Wissenchaftliche Verlagsgesellschaft mbH, Stuttgart, Germany.

3. CHEMICAL CHARACTERIZATION, ANALYTICAL METHODS AND THE DEVELOPMENT OF SPECIFICATIONS

3.1 Introduction

Chemical characterization plays a critical role in risk assessment, in surveys and in regulatory monitoring activities. Suitable analytical methods are necessary for:

- the definition of the nature, including isomeric composition and chemical purity, of the materials investigated during in vitro and in vivo hazard identification and characterization studies;

For acronyms and abbreviations used in the text, the reader may refer to the list of acronyms and abbreviations at the front of this monograph. Definitions of select terms may be found in the glossary at the end of the monograph.

- the speciation of contaminants (e.g. determination of the various chemically bonded forms of elements);
- determination of the concentrations of the chemical under review and its relevant metabolites and breakdown products in body fluids, tissues and excreta of laboratory animals and of food-producing animals in pharmacokinetic/toxicokinetic and residue depletion studies;
- determination of the concentrations of contaminants and of incurred residues of veterinary drugs and pesticides of concern; and
- the identification and quantification of the substances for which maximum residue limits (MRLs) and maximum levels (MLs) are recommended by the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).

Analytical requirements of JECFA and JMPR for food additives, pesticides, veterinary drug residues, contaminants and substances consumed in large amounts are given in sections 3.4, 3.5, 3.6, 3.7 and 3.8, respectively.

Chemical characterization is also necessary for the preparation of specifications for the identity and purity of food additives.

3.2 Criteria for the review of analytical methods and required technical competence of testing laboratories

At the time of the review of the analytical methods by JECFA and JMPR, they must at least have been validated in accordance with accepted criteria of single-laboratory validation carried out by a laboratory accredited according to the applicable international standard for testing laboratories or operating an equivalent system of quality management and exhibiting equivalent technical competence.

JECFA and JMPR review the suitability of the methods on the basis of the available validation data. Therefore, the methods should be described in an internationally recognized format, and the information on method validation should include the data generated in the process of determining the following performance characteristics: specificity,

limit of detection (LOD), limit of quantification (LOQ), accuracy and precision (repeatability within the laboratory). A mathematical/statistical description of calibration curves should also be given if such curves form the basis for the quantification of the analytes. Definitions and interpretations of the above performance characteristics, requirements with regard to single-laboratory validation and further references to relevant Codex Alimentarius Commission (CAC) documents are provided and regularly updated in the Procedural Manual of CAC, which is published on its web site (FAO/WHO, 2008). However, JECFA and JMPR always review the above performance characteristics in the light of contemporary scientific and technical development.

For methods developed solely for the purpose of generating the database required for the risk assessment, every suitable analytical approach is acceptable. However, methods recommended for monitoring of compliance of commodities with recommended regulatory limits should meet additional criteria, such as applicability, practicability and ruggedness. For such methods, the validation study must also include the analysis of incurred residues in a suitable number of independent tissues or commodities. The definitions of these criteria are subject to change in view of the rapid progress observed in the development of analytical technology, including instrumentation. JECFA and JMPR carry out a full scientific review with regard to these additional criteria. A further evaluation with regard to collateral criteria is carried out by the competent CAC committees—the Codex Committee on Methods of Analysis and Sampling (CCMAS), the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) and the Codex Committee on Pesticide Residues (CCPR).

It is known that methods based on certain principles, such as microbiological inhibition or ligand–protein interactions in the determinative step of a method, cannot meet all of the above criteria. If such methods are proposed, JECFA and JMPR will review them on a case-by-case basis and discuss them in sufficient detail in the monographs prepared to enable national authorities to judge whether these methods could serve as screening methods in monitoring programmes.

The currently applicable international standard laying down the general requirements for the competence of testing and calibration laboratories is the norm ISO/IEC 17025 (ISO, 2005). If laboratories

comply with the requirements of this international standard, which incorporates relevant elements of Good Laboratory Practice (GLP), they will operate a quality management system for their testing and calibration activities that also meets the quality management principles of ISO 9001 (ISO, 2008). An important additional requirement for obtaining and maintaining accreditation is the regular successful participation in proficiency tests. JECFA and JMPR will judge on a case-by-case basis whether the infomation on method validation provides sufficient evidence that it has been carried out under conditions equivalent to those required by the above-mentioned international standard and whether partial absence of such evidence has an impact on the credibility of the results of the validation.

3.3 The significance of multilaboratory method trials and collaborative studies

Relatively few of the analytical methods reviewed by JECFA and JMPR have been subjected to properly designed multilaboratory studies, which provide information on method performance in the hands of different analysts in different laboratories. In view of the currently established framework for single-laboratory validation, it is generally not necessary to conduct multilaboratory studies in order to enable JECFA and JMPR to review and assess analytical methods with regard to fitness for purpose. If such studies are performed, the international harmonized protocol agreed upon by the competent international organizations (Thompson & Wood, 1993) should be followed. However, JECFA and JMPR will perform an independent review of available studies based on an accurate record of the design and conduct of the study and the raw concentration data obtained in the analysis of the samples used in the study.

Multilaboratory trials that do not meet all criteria for the conduct of collaborative studies and subsequent statistical evaluation of the results may still provide useful information on the expected performance of the method tested.

Multilaboratory and collaborative studies of methods usually do not encompass all possible combinations of the analyte and commodities for which regulatory limits have been recommended and to which the method may subsequently be applied. These methods may

be extended to related analytes and sample materials not included in the original multilaboratory study by completing additional properly designed within-laboratory studies, provided such activities are covered by the scope of the accreditation of the laboratory involved. JECFA and JMPR will review all available information with a view to scientifically assess the fitness for purpose of a method.

3.4 Food additive specifications

3.4.1 General considerations

Specifications of identity and purity are necessary products of JECFA safety evaluations for food additives. Evaluations of food additives by JECFA depend on studies performed with a chemical substance or product of defined identity, purity and physical form. The acceptable daily intake (ADI) is valid only for products that do not differ significantly in identity and quality profile from the material used to generate the data used in the evaluation.[1]

The specifications of identity and purity established by JECFA are intended to ensure that the Committee's safety evaluations apply, with a high degree of confidence, to all products manufactured to comply with those specifications. The first Joint FAO/WHO Conference on Food Additives (FAO/WHO, 1956) was asked to formulate general principles governing the use of food additives and to recommend suitable methods for the chemical, physical, pharmacological, toxicological and other properties of individual food additives.

The first two meetings of JECFA prepared reports on general principles governing the use of food additives (FAO/WHO, 1957) and procedures for the testing of intentional food additives to establish their safety for use (FAO/WHO, 1958) and recommended the need for specifications. Since then, specifications have been an important part of JECFA evaluations of food additives. JECFA specifications have three purposes:

[1] For an overview of the purpose, function and format of JECFA food additive specifications and the interaction of JECFA and CAC, see the introduction to the Combined Compendium of Food Additive Specifications (FAO, 2005/2006).

1) to identify the substance that has been tested biologically;
2) to ensure that the substance is of the quality required for safe use in food; and
3) to reflect and encourage Good Manufacturing Practice (GMP) and maintain the quality of additives on the market.

Since 1956, the meetings of JECFA have designated specifications as either full or tentative. Until the twenty-third meeting of JECFA, specifications were designated as tentative either because the chemistry data were inadequate or because a temporary ADI was assigned to the additive. At and since the twenty-third meeting of JECFA, a tentative specification has been assigned only when the data were inadequate for preparing full specifications.

A food additive may be a single chemical substance, a manufactured chemical mixture or a natural product. Complete information on chemical composition—including description, methods of manufacture, raw materials and impurities—is equally important for each type of additive. However, implementation of the requirement for chemical composition data may vary, depending on the type of substance.

For additives that are single chemical substances, it is virtually impossible to remove all impurities arising from their commercial production; therefore, analyses are generally performed on the major component and predicted impurities, especially those with potential toxicity.

For commercially manufactured complex mixtures, such as monoglycerides and diglycerides, information is needed on the range of substances produced, with emphasis on descriptions of manufacturing processes, supported by analytical data on the components of the different commercial products.

Natural products present particularly difficult problems because of their biological variability and because the chemical constituents are too numerous for regular analytical determinations. For additives derived from natural products, it is vital that the sources and methods of manufacture be defined precisely. Chemical composition data should include analyses for general chemical characteristics. These might include proximate analyses of protein, fat, moisture, carbohydrate

and mineral content. Analyses should be undertaken for specific toxic impurities carried over from raw materials or chemicals used in the manufacture of the product. Further information necessary for the evaluation of substances used in large amounts, which are often derived from natural products, is provided in section 3.8.

JECFA policy has been to prepare specifications whenever constituents of the substance added to food had the potential to be present in the finished food. Initially, specifications were prepared only for intentional food additives—that is, those that are added directly to a food to accomplish a technical effect (e.g. a preservative or colour). The fourteenth meeting of JECFA (FAO/WHO, 1971) prepared specifications for extraction solvents; although these "processing aids" are largely removed from food, evaluation of their safety in use depends on their identity and purity. Since then, specifications have been prepared for all processing aids (e.g. antifoaming or clarifying agents, enzyme preparations, filtering aids, packing gases, release agents and others) used in conjunction with food manufacture.

The twenty-seventh meeting of JECFA (FAO/WHO, 1983) decided that chemical reagents used in the preparation of food additives or processing aids (e.g. glutaraldehyde in the preparation of immobilized enzyme preparations or acetic anhydride in the manufacture of modified starches) do not usually need specifications. Carryover of these reagents or their contaminants into food may be controlled by the specifications for purity of the specific additive or processing aid.

Many food additive specifications have identical analytical methods or test procedures. To avoid repetition in each individual specification, these methods and test procedures were assembled in a volume entitled "Guide to Specifications" (FAO, 1978), and subsequent specifications referred to that volume when appropriate. The volume was revised and updated in 1983 (FAO, 1983) and 1991 (FAO, 1991). In 2006, the information contained in the volume was completely revised and rewritten and was published as Volume 4 of the Combined Compendium of Food Additive Specifications (FAO, 2005/2006).

Food additives may be marketed as formulated preparations, such as a mixture of a main ingredient with a solvent vehicle and emulsifier. Specifications refer to each ingredient in the formulated preparation

as individual commercially manufactured food additive substances. Mixtures should not be formulated in such a way that the absorption or metabolism of any ingredient is altered; otherwise, the biological data, derived using the individual component, will be invalidated (FAO/WHO, 1966, 1972). Added substances, such as anticaking agents, antioxidants and stabilizers, may influence the results of analytical tests given in specifications. Therefore, in its nineteenth report, JECFA recommended that manufacturers of food additives should indicate the presence of such added substances (FAO/WHO, 1975).

3.4.2 Formulation of specifications and information requirements

The formulation of satisfactory specifications requires that detailed information be made available to JECFA on the method of manufacture of the additive, including information on raw materials and on its chemical characterization. The Committee requires such information to be provided as part of the total data package whenever an additive is submitted for risk assessment; all such information is regarded as suitable for being made publicly available unless requested otherwise and agreed by the JECFA Secretariat. Those submitting data for a JECFA evaluation are advised to consult existing specifications for further guidance, which is available in the Combined Compendium of Food Additive Specifications (FAO, 2005/2006), where the individual criteria used in the elaboration of JECFA specifications are described. The same criteria are used for most additives; however, because of their particular characteristics, separate criteria have been developed for enzyme preparations and for flavouring substances.

Specifications may be revised when there is new information available on methods of manufacture or on the characteristics of the product or when changes or revisions in analytical methods are needed. Such specification changes may trigger a review of the safety evaluation; conversely, a review of the specifications may be needed if the safety is re-evaluated.

Although all the individual criteria in specifications monographs must be met, additives are mainly defined by a combination of 1) a description of their manufacture, 2) a minimum requirement for the content of the principal functional components of the additive and 3)

maximum limits for undesirable impurities. The relative importance of these criteria depends on the nature of the additive; for example, additives composed largely of single components are mainly defined in terms of their chemical purity, whereas the definition of more complex materials relies more on a description of the raw materials and the method of manufacture.

3.4.3 Stability and fate of additives in food

Specifications are intended to apply to the additive as marketed and supplied for food use. In considering whether specifications apply to food additive quality as manufactured or as added to food, JECFA has decided to prepare specifications to cover the normal shelf-life of the additive. Limits are set for decomposition products that may form during normal storage. Manufacturers and users of food additives should ensure good packaging and storage conditions and use good handling practices to minimize deleterious changes in quality and purity (FAO/WHO, 1975). Information on changes in the composition of food additives during storage should be submitted for evaluation by the Committee.

Certain food additives perform their functional effect by reaction with undesirable food constituents (e.g. antioxidants react with oxygen in food, and ethylenediaminetetraacetic acid [EDTA] reacts with trace metals) or by reactions that modify food constituents (e.g. flour improvers). Food additives may also degrade under certain conditions of food processing, even though such degradation is detrimental to their functional effect. For example, the sweetener aspartame is transformed to a diketopiperazine derivative at rates that vary with the acidity and the temperature of the food. For such additives, the Committee has evaluated analyses for additive reaction products in food as consumed and biological testing data on either specific reaction products or samples of food containing the reaction products as consumers would ingest them.

In order to ensure that test data are relevant to the way in which the additive is used in food, the Committee requires information on potential reactivity to be provided as part of submissions for the safety evaluation of all intentional food additives (FAO/WHO, 1981). Four types of data related to reactivity are required:

1) the general chemical reactivity of the additive;
2) stability of the additive during storage and reactions in model systems;
3) reactions of the additive in actual food systems; and
4) the metabolism of the additive in living organisms.

These data are important for relating toxicological data to the actual use of the additive in food.

Processing aids are substances that come into contact with food during processing and may unintentionally become part of food because of their incomplete removal. JECFA has evaluated a number of processing aids, such as extraction solvents and enzyme preparations, for their safety in use. When evaluating a processing aid, information should be provided on its use and either analytical data on or a computed estimate of the amount of the processing aid carried over into food. Particular attention should focus on any component of the processing aid that may have the potential for biological effects, such as ethylenimine leaching from polyethylenimine, an immobilizing agent used in the preparation of immobilized enzyme preparations.

3.4.4 Analytical methods

Information submitted to JECFA on the identity and purity of food additives should always include details of the analytical methods that can be used to verify the information. Information on the potential compositional variability of the substance should also be given, together with details of any sampling protocols used to assess this. Insufficient information on analytical methodology is one reason why JECFA may be unable to elaborate suitable specifications or why it may decide that it is able to assign only a "tentative specification" pending receipt of the further information required.

JECFA specifications incorporate guidance on the analytical techniques that should be used to verify the information. Wherever possible, this should be done by reference to Volume 4 of the Combined Compendium of Food Additive Specifications (FAO, 2005/2006). If this is not possible, details of the test procedures are set out in the individual specifications monographs.

Because JECFA specifications are elaborated for worldwide use, the Committee prefers to quote methods that require the use of apparatus and equipment that are available in most laboratories, provided that such methods give results appropriate to the specified criteria. Methods involving more recently developed techniques or equipment will therefore not normally be quoted until such techniques are accepted internationally and are generally available at reasonable cost. However, reference to specific methods of analysis should not be taken as precluding the use of other methods, provided that these are validated as giving results of at least equivalent accuracy and specificity to those quoted.

3.5 Pesticide characterization

3.5.1 General considerations

When an active ingredient is evaluated by JMPR for the first time or during a periodic review, it is identified by its International Organization for Standardization (ISO) common name, International Union of Pure and Applied Chemistry (IUPAC) and Chemical Abstracts Service (CAS) systematic chemical names, CAS and Collaborative International Pesticides Analytical Council (CIPAC) numbers, structural formula (with stereochemistry when needed), molecular formula and relative molecular mass.

For relatively pure synthetic compounds, the identity is straightforward, but for isomer mixtures, clear identification needs special attention. A CAS number is not necessarily a unique identifier for a compound, even for a specific isomer. Information is required on the proportions of different components when the compound is a mixture (e.g. of stereoisomers), because the isomers may have different toxicological properties (Green, 1978; FAO/WHO, 1980). For example, an ADI for permethrin (40% *cis* : 60% *trans*) was allocated in 1982 (FAO/WHO, 1982), whereas an ADI for permethrin (25% *cis* : 75% *trans*) was not allocated until 1987 (FAO/WHO, 1987).

The considerations of identity, purity and stability of pesticides were explained in chapter 4 of Environmental Health Criteria (EHC) 104 (IPCS, 1990). Toxicological evaluations are strictly valid only for the technical-grade material being examined, and special care and

knowledge of the detailed specifications are required to extrapolate the findings to other products.

The 1987 JMPR (FAO/WHO, 1987) noted that ADIs based on studies using compounds of specific purity can be relevant to products of different origin or purity (i.e. equivalent products), but that there are examples where changes in the amount or type of impurity in the technical material can markedly influence the toxicity of a compound.

The International Code of Conduct on the Distribution and Use of Pesticides (FAO, 2005) defines equivalence broadly as:

> the determination of the similarity of the impurity and toxicological profiles, as well as of the physical and chemical properties, presented by supposedly similar technical material originating from different manufacturers, in order to assess whether they present similar levels of risk.

JMPR (FAO/WHO, 1985), after noting the influence on toxicity of impurities such as dimethylhydrazine, dioxins and hexachlorobenzene, stressed "the importance of determining whether the toxicity of a technical pesticide is due to the inherent toxicity of that compound or also due to the presence of toxic impurities".

In 1999, FAO, in cooperation with WHO, introduced a revised procedure for evaluating data to establish specifications for pesticides (FAO/WHO, 1999c). The Joint FAO/WHO Meeting on Pesticide Specifications (JMPS) now establishes specifications for technical-grade material and formulations. The specifications include minimum permitted content of active ingredient and maximum permitted concentrations for relevant impurities. A relevant impurity is a by-product of the manufacture or storage of a pesticide that, compared with the active ingredient, is toxicologically significant to health or the environment, is phytotoxic to treated crops, causes taint in food crops, affects the stability of the pesticide or causes any other adverse effect. The long-term aim was for FAO/WHO specifications for technical material to be developed before the establishment of an ADI or an acute reference dose (ARfD).

Data required to support the development of pesticide specifications by JMPS include the identity of the active ingredient, physical and chemical properties, route of manufacture, minimum active

ingredient content, maximum limits for impurities present above 1 g/kg, maximum limits for impurities proposed as relevant at <1 g/kg, the identity and nominal content of compounds intentionally added to the technical material, toxicological and ecotoxicological summaries, properties of formulations, and methods for the analysis and testing of technical material and formulations (includes methods for relevant impurities).

A IUPAC project examined the significance of impurities in the safety evaluation of pesticides and made recommendations on assessment, analysis and monitoring of pesticide quality (Ambrus et al., 2003).

JMPR takes account of the JMPS specifications for a pesticide where available. In other cases, the technical-grade pesticide is characterized by its minimum purity, isomer composition and the limits for content of impurities that might impact on the hazard assessment. Because data on impurities and the composition of technical-grade materials could provide valuable information to competitors, they are normally confidential information and are not published in the JMPR reports or monographs. In 2005, JMPR reiterated the previous conclusions that specifications for the technical material should be developed for a pesticide before it is evaluated within the periodic review programme of the CCPR and for new pesticides, but that this should not delay evaluation of pesticides by JMPR (FAO/WHO, 2005a).

Data on the shelf-life stability of the technical-grade material are also important, because the percentage of the active material will decrease and that of potentially relevant breakdown products may increase with time if a test compound is unstable under the conditions of storage.

As well as the importance of possible changes in products offered for sale, shelf-life stability may be critical in studies where a single batch of technical material is utilized for a long-term study or a multigeneration study. Also, variable percentages of degradation occurring in different batches (i.e. batches of different post-manufacturing age) may complicate the interpretation of a study. Further, components of the test diet might promote degradation of the active compound, which may result in the production of toxic reaction products in the diet. In

cases where the percentage of active parent compound decreases or the breakdown products are more toxic than the parent compound, no-observed-adverse-effect levels (NOAELs) derived from the toxicity tests may not be representative of the product as used.

To date, JMPR has evaluated only the active ingredients (pure and technical grade) of pesticide formulations. The toxicity of other ingredients of the formulations—such as solvents, emulsifiers and preservatives—that may occur as residues in food has not been considered.

3.5.2 Identity and purity

Guidance on the development and use of specifications for pesticides evaluated by JMPR was elaborated in 2002 by the first meeting of JMPS (FAO/WHO, 2002) and updated in 2006 (FAO/WHO, 2006a).

For the purposes of the characterization:

- A detailed specification of the test material used in each individual study must be provided.
- Where isomeric mixtures exist, the ratio of isomers in the test material must be clearly specified.

For purity considerations:

- The percentage of the active ingredient in any technical material used in a toxicity test or proposed for marketing must be specified.
- Percentages of all identifiable impurities should be specified.
- Data on manufacturing processes may be required to permit determination of potential impurities; however, because of confidentiality, such data will not be published in JMPR monographs.

3.5.3 Stability

The stability of the test material during storage and in the diet must be adequately investigated and reported.

Where instability in diets is observed, the possible reaction products and the nutritional quality of the diet should be investigated.

3.5.4 Physical and chemical properties

Data submitted on the physical and chemical properties of the pure active ingredient are evaluated in order to recognize the influence of these properties on the behaviour of the pesticide during and after its application on crops or animals. JMPR receives data on the pesticide's physical appearance, solubility in water (including pH effects) and in organic solvents, vapour pressure, dissociation constant, *n*-octanol–water partition coefficient (K_{ow}), hydrolysis and photolysis.

The volatility of the compound, its stability in water and its sensitivity to irradiation with ultraviolet light may considerably affect its disappearance after application.

Epimerization may sometimes be observed during hydrolysis studies. For example, esfenvalerate (2S,αS) was epimerized to the 2S,αR isomer more quickly than it was hydrolysed under experimental conditions (FAO, 2003). The proportion of epimers may influence the toxicity.

The solubility of the pesticide is of great importance, because the ability of the compound to penetrate plant and animal tissues is dependent on its solubility in water and organic materials.

JMPR (FAO/WHO, 1991) chose the K_{ow} of a pesticide as the physical property to represent solubility in fat. In general, the compound would be designated fat soluble when log K_{ow} exceeded 4, but not when log K_{ow} was less than 3. Subsequently, JMPR (FAO/WHO, 2005b) examined the available data and concluded that partitioning in meat between fat and muscle is essentially independent of log K_{ow} for compounds with values greater than 3. In consequence, and when no evidence is available to the contrary, the compound is designated fat soluble when log K_{ow} exceeds 3, but not when log K_{ow} is less than 3. Although log K_{ow} of an individual component of a residue is an initial indicator, it is not the only or prime factor used to assess fat solubility. The distribution of the residue (as described in the residue definition) between muscle and fat obtained from livestock metabolism and feeding studies should be the prime indicator of fat solubility.

3.5.5 Analytical methods

Pesticides are very diverse chemical compounds with a wide range of physical and chemical properties. Analytical chemists have devised methods for the analysis of pesticide residues, including their transformation products, in a wide range of situations.

Methods should be validated to provide the supporting information on accuracy, selectivity and reliability of the data generated by the method. Hill & Reynolds (1999) explained the practicalities and compromises in validating analytical methods for pesticide residues in food and animal feeds.

Analytical methods should be suitable for the required purpose, which usually falls into one of three areas of residue analysis:

1) data generation for registration;
2) MRL enforcement and surveillance; and
3) total diet studies.

JMPR evaluates the analytical methods used for generation of residue data to check that the methods are suitable for the relevant analytes and sample types. The methods should be supported by adequate validation data, especially on analytical recoveries, LOQ and selectivity.

JMPR also reports information on methods that are suitable for MRL enforcement and whether particular compounds are suitable for analysis by multiresidue methods.

Most analytical methods for residues of simple organic compounds in a food commodity matrix consist of three main steps: 1) extraction, 2) cleanup and 3) determination or measurement, usually involving gas chromatography or liquid chromatography. However, some analytes require other approaches. For example, a chemical reaction may be needed to release an analyte from the residue, or a derivative of the analyte may have to be prepared for the chromatography step (e.g. the analytical method for residues of dithiocarbamates is nonspecific and measures carbon disulfide released by treatment with acid).

JMPR evaluates methods used for generating preregistration residue data that are needed for analysis of samples from:

- supervised residue trials;
- food processing studies;
- livestock feeding studies and direct animal treatment; and
- sample storage stability studies.

Analytes include compounds to be specified in the residue definitions (i.e. the MRL enforcement residue definition and the dietary intake risk residue definition). This substance would, in the majority of cases, be the parent compound, with inclusion of one or more metabolites or other transformation products when appropriate, based on the metabolism of the pesticide in plants and animals.

The LOQ of the analytical method for residue trials would be typically 0.01–0.05 mg/kg. Lower LOQs may be needed in some circumstances. For example, dietary intake calculations for a pesticide with a low ADI or ARfD might suggest that residues need to be measured at levels less than 0.01 mg/kg, necessitating a method with a lower LOQ. Total diet studies may need especially low LOQs for some analytes.

The FAO Panel of JMPR defines the LOQ of an analytical method for residues in specified commodities as being the lowest level where satisfactory recoveries were achieved. The LOQ is the smallest concentration of the analyte that can be quantified. It is commonly defined as the minimum concentration of analyte in the test sample that can be determined with acceptable precision (repeatability) and accuracy under the stated conditions of the test (FAO, 2002b).

Analytical recovery data support JMPR decisions on the acceptability or non-acceptability of the associated residue data. Recoveries in the 70–120% range are considered satisfactory. JMPR does not normally adjust or correct residue data using analytical recovery data.

Residue methods should normally be tested and validated on representative commodities (chosen because of expected residue occurrence), such as:

- plant material with a high moisture content (e.g. lettuce, tomatoes);
- plant material with high oil and protein contents (e.g. soybeans, peanuts, avocados);

- plant material with high starch or sugar content (e.g. cereal grains, potatoes);
- acidic commodities (e.g. citrus fruits);
- low-moisture feed materials (e.g. maize fodder);
- animal tissues (e.g. beef muscle, fat, liver, kidney); and
- milk and eggs.

Some matrices may cause particular problems (e.g. poor recoveries or interferences). For example, onions, broccoli and cabbage release carbon disulfide from endogenous precursors when treated with acid, which interferes with the measurement of dithiocarbamate residues (FAO, 1993a). In another example, recoveries of approximately 50% were obtained when racemic glufosinate was spiked into transgenic glufosinate-tolerant soybean plants, because the transgenic plant material very rapidly metabolized the L-enantiomer, leaving only the D-enantiomer for measurement (FAO/WHO, 1999b).

Interference from the matrix could add to the measured residue or cause losses during the procedure, and such problems are often encountered. For example, the chromatographic response to indoxacarb residues was enhanced by the crop extract, necessitating the preparation of standard solutions in crop extract (FAO, 2006).

The analysis of ethylenethiourea residues in the presence of parent ethylenebisdithiocarbamate (mancozeb) presents special problems that may not be covered by normal validation testing. Mancozeb residues may be converted to ethylenethiourea under some conditions during the analytical procedure (estimated conversion rates 0.22–8.5%). In samples where mancozeb is present at concentrations up to 1 mg/kg, it is possible that ethylenethiourea residues close to but above the LOQ (0.02 mg/kg) may have been produced during the analytical procedure (FAO, 1993b).

The extraction efficiency for residues bound within the matrix cannot be tested by spiking samples shortly before analysis, but bound ^{14}C-labelled residues from metabolism studies may be used to check extractability. Samples of plant and animal tissue from the radiolabelled metabolism studies containing bound ^{14}C residue levels may subsequently be analysed by the routine residue method (or, at least, the extraction procedure of the routine method) in order to define the extractability of the bound ^{14}C residues.

The 1998 JMPR (FAO/WHO, 1999a) recommended that

> Comparative extraction efficiency studies including the frequently used extraction solvents, such as acetone/water, ethyl acetate and acetonitrile/water should be carried out on samples from metabolism studies for the compounds which are expected to be included in the residue definition(s).

A IUPAC report (Skidmore et al., 1998) stated that

> The extraction procedures used in residue analytical methods should be validated using samples from radiolabelled studies where the chemical has been applied in a manner consistent with the label and Good Agricultural Practices.

In analytical chemistry, the term "common moiety" means that structural portion of different compounds that is the same and that tends to remain intact during chemical reactions. A common moiety analytical method relies on this feature to measure the concentration of a group of related compounds all together. Such a method may be useful when a number of metabolites with the common moiety need to be included in the estimates of dietary intake or when the composition of the residue is quite variable and the common moiety is easier to measure than a specific component. An example of this is the analysis of dithiocarbamate pesticides using acid-release carbon disulfide as the final analyte.

An analytical method used for testing the stability of residues during frozen storage needs to be reproducible for the duration of the test (perhaps 2 years), and it should distinguish the starting compound from degradation products. If analytical recoveries are too variable, the variability will obscure conclusions about stability, and only large losses during storage will be observable.

3.6 Veterinary drug residues

3.6.1 General considerations

The basic data requirements were established by the thirty-second meeting of JECFA (FAO/WHO, 1988). The Committee must be assured that any veterinary drug it evaluates is well characterized, with details of the chemical and physical properties of the drug and the identity

and concentrations of any major impurities. In addition, the manufacturing process should be described and the consistency and quality of the final products demonstrated. This information should be included in the dossier submitted for review by the Committee and is used to define the substance used in the studies that lead to the establishment of the MRLs for a veterinary drug (MRLVDs)[1] and the ADI.

Veterinary drugs cover a broad range of chemical structures and usually undergo metabolism after administration to an animal. Modes of administration include injection, implantation, dermal application by spray or pour-on, and inclusion in feed or water, all of which may result in different rates of absorption, with possible differences in the tissue distribution and nature of the residues. The form and the distribution of the residues that result from each authorized mode of application in each species should be determined, and the depletion of the residues from edible tissues or animal-derived foods should be studied. A marker residue should be identified, which is usually the form of the drug (parent compound or metabolite) that is found at the highest concentration for the longest period in the target food. The relationship of this marker residue to the total residue of the drug should be determined, usually through treatment of experimental animals with an isotope-labelled form of the drug. The tissue in which the highest residues are found is usually designated as a "target tissue" for routine monitoring purposes.

Analytical methods, whether intended for use in pharmacokinetic and metabolism studies, in residue depletion studies or in regulatory control programmes for residues of veterinary drugs, share a common subset of validation criteria. However, additional criteria are to be met for methods used in routine monitoring of compliance of commodities with MRLVDs. Performance characteristics to be determined for all methods include specificity, accuracy, precision, LOD, LOQ, susceptibility to interference and information on method calibration. Practicability, applicability under normal laboratory conditions and ruggedness are the additional criteria for the evaluation of regulatory methods. Validation thus addresses all aspects of performance

[1] Both JECFA and CCRVDF use the acronym MRL for this limit throughout its stepwise elaboration; however, MRLVD is the acronym of the final standard adopted by CAC on the recommendation of CCRVDF.

characteristics of the analytical methods. Target values for method precision and recovery have been established by CCRVDF for the concentrations typically required to support MRLVDs (FAO/WHO, 1993).

3.6.2 Analytical methods

The first meeting of the Committee devoted exclusively to the evaluation of veterinary drugs (FAO/WHO, 1988) recognized that analytical methods are required to

> detect, quantify and positively identify residues of veterinary drugs; support toxicological, drug metabolism, and pharmacokinetic studies; support residue studies of compounds to be evaluated by the Committee; and satisfy the needs of public health agencies.

The initial focus of JECFA was to ensure that methods used in the pharmacokinetic and residue depletion studies evaluated by the Committee had been suitably described and appropriately validated. The ninth session of CCRVDF decided that no MRLVD could be accepted without a suitable method being identified to support the MRLVD. This decision added emphasis to the role of JECFA in identifying analytical methods suitable for regulatory use as part of their review (FAO/WHO, 1997). The eleventh session of CCRVDF (FAO/WHO, 1999d) determined that JECFA would have primary responsibility for review of methods for compounds. This was taken into account at the fiftieth (FAO/WHO, 1999e) and all subsequent meetings of JECFA. A guidance document entitled "JECFA Requirements for Validation of Analytical Methods" was published with the residue monographs of the fifty-eighth meeting of JECFA (FAO, 2002a).

During JECFA review, the primary requirement for methods used in pharmacokinetic and residue depletion studies is that the method has been shown to have performed reliably in the hands of the analyst or analysts involved in that specific study. The dossier reviewed by JECFA usually includes a complete validation report for the method, particularly if the method has not been published in the peer-reviewed scientific literature.

For some compounds evaluated by JECFA, no residues were detected in one or more of the four edible target tissues (muscle,

liver, kidney, fat) from any of the animals to which the drug had been administered at any time of sampling. In such cases, CCRVDF has requested that JECFA establish MRLVDs for these tissues in which no residues have been detected, based on the LOQ of the available residue control method, provided that such MRLVDs are consistent with adequate health protection.

In the past, JECFA and CCRVDF have not usually recommended analytical methods for residues of substances for which no ADI or MRLVD has been established. This practice has since been changed, and the Committee now recommends validated methods for substances without a recommended ADI or MRLs, provided such methods are made available to the Committee.

3.7 Contaminants

3.7.1 General considerations

Contaminants in the diet may include environmental pollutants, such as heavy metals and industrial chemicals, mycotoxins, migrants from packaging materials and other substances not authorized for use in food.

The data required for the characterization of a contaminant should include its concentrations in foods and the total diet from as many countries as possible. The sixty-fourth meeting of JECFA (FAO/WHO, 2006b) recommended that the data should be formatted using the Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) to facilitate the collation and quality control of the data. The data should be accompanied by additional details on sampling plans and analytical methods used to generate the data.

Contaminants in food commodities may result from environmental contamination by persistent compounds formerly used as pesticides (e.g. persistent organochlorine pesticides). JMPR proposes limits (extraneous maximum residue limits [EMRLs]) for such contaminants when they originate from environmental sources and not from direct or indirect uses on the crop or farm animals. In 1990 (FAO/WHO, 1990), JMPR explained that EMRL assessments rely on monitoring data and supporting information, including:

- country;
- year;
- commodity and portion analysed;
- pesticide and residue definition;
- sample classification as import, export or domestic production and consumption; and
- sampling plan described as random monitoring or target sampling.

Ideally, for reasonable EMRL estimates to cover international trade, JMPR should have current and geographically representative data (FAO/WHO, 1996), but typically data are available from only three or four (usually developed) countries. JMPR requests the submission of all relevant data, including nil results. Because residues gradually decrease, new data should be assessed every few years with a view to EMRL revision.

3.7.2 Analytical methods

The LOQs of the analytical methods to measure the concentrations of contaminants in foods (on a raw basis or an as consumed basis) should be as low as reasonably possible (usually much lower than the regulation limit). This consideration is of critical importance in exposure estimations, because low levels of contaminants are frequently present in foods, and the censored data (data points with non-quantified results) represent a bias source in calculations of exposure. If the LOQ is not sufficiently low, then there is a risk of underestimation if all non-detects are taken as zero or overestimation if all non-detects are taken as the LOQ. To minimize this bias, it is recommended that the censored data should be treated following the statistical approach discussed in chapter 6.

3.8 Substances consumed in large amounts

Thorough chemical analysis should be performed on high-consumption substances, such as bulk additives, to measure potential impurities and to provide information on nutritional adequacy, especially when such substances replace traditional food.

It is not possible to provide a checklist of necessary chemical studies to cover all high-consumption compounds. The substance should

be subjected to a full analysis, and particular attention should be paid to the points discussed in the following paragraphs.

Because the exposure to undesirable impurities (e.g. heavy metals) concomitant with the intake of high-consumption materials is potentially high, special effort should be made to identify the impurities. Information on the production process, including the materials and procedures involved, will point to the types of contaminants for which limits may need to be specified. The specifications should be accompanied by details of product variability and of the analytical methods used to check the specifications and details of the sampling protocols. If the substance is so complex that comprehensive product specifications on chemical composition are impracticable (as they might be for a microbial protein), the description of the substance in the specifications may include relevant aspects of its manufacturing process. If manufacturing data are based on production on a pilot scale, the manufacturer should demonstrate that, when produced in a large-scale plant, the substance will meet the specifications established on the basis of pilot data.

The permissible limits for impurities may in some cases correspond to the levels accepted for natural foods that have similar structure or function or that are intended to be replaced by the new material. If the substance is prepared by a biological process, special attention should be paid to the possible occurrence of natural toxins (e.g. mycotoxins).

If the nature of the substance or manufacturing process indicates the possible presence of naturally occurring or adventitious anti-nutritional factors (phytate, trypsin inhibitors, etc.) or toxins (haemagglutinins, mycotoxins, nicotine, etc.), the product should be analysed for them specifically. Biological tests, either as part of the nutritional evaluation in the case of enzyme inhibitors or more specifically as part of a mycotoxin screening programme, will provide useful backup evidence concerning the presence or absence of these contaminants.

Finally, if under the intended conditions of use the substance may be unstable or is likely to interact chemically with other food components (e.g. degradation or rearrangement of the substance during heat processing), data should be provided on its stability and reactivity. The various tests should be conducted under conditions relevant to the use

of the substance (e.g. at the acidity and temperature of the environment and in the presence of other compounds that may react).

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