The Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives and Its Role in the Evaluation of the Safety of Veterinary Drug Residues in Foods

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ABSTRACT

The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) recommended the evaluation of food additives at the international level through the establishment of an expert committee or committees. These committees evaluated the safety of food additives present as residues resulting from the use of pesticides or veterinary pharmaceuticals. The results of these meetings include international harmonization on acceptable daily intake of these compounds and the maximum residue limit that is permitted to be present within any food of animal or plant origin. The decisions rendered by these committees provide a key element in the elimination of international trade barriers associated with products intended for human consumption.

KEYWORDS: human food safety, international harmonization, maximum residue limit, acceptable daily intake, World Health Organization, Codex Alimentarius, JECFA.

BACKGROUND

In 1955, a joint conference in Geneva sponsored by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) recommended the evaluation of food additives at the international level through the establishment of an expert committee or committees. These committees were to be convened jointly by the directors general of FAO and WHO to provide an independent expert review and recommendations with respect to such

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compounds. The first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome in 1956 to evaluate the safety of food additives, with the role later broadened to include the evaluation of contaminants, natural toxins, and veterinary drug residues. A companion expert committee, the Joint Meeting on Pesticide Residues (JMPR), first met in 1963 to provide expert advice on pesticide residues in foods.

JECFA and JMPR are independent committees, convened under formal rules established by FAO and WHO for the appointment and conduct of expert committees. They are independent of the Codex Alimentarius Commission and its committee structure but are closely associated with the work of certain subject committees within the Codex Alimentarius system. The Codex Alimentarius Commission was created in 1961 by FAO, with support from WHO, the Economic Commission for Europe (ECE), the Organization for Cooperation and Development (OECD), and the Council of the Codex Alimentarius Europaeus, created in Europe in the 1950s to provide a regional food code. A Joint FAO/WHO Food Standards Conference in 1962 recommended the formation of a joint FAO/WHO food standards program, the Codex Alimentarius. The World Health Assembly approved this recommendation in 1963.

The 12th JECFA Meeting in 1968 dealt with issues related to the use of antimicrobial agents in food animals.¹ Subsequent meetings primarily considered food additives or contaminants, until the 25th, 26th, and 27th Meetings of JECFA, which, while dealing primarily with food additives, also began the evaluation of xenobiotic anabolic agents.²⁻⁴ However, a Joint FAO/WHO Expert Consultation, held in 1984, recommended both the establishment of a Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) and the convening of an ad hoc expert scientific body to advise member governments and the new Codex Committee on public health and international trade issues related to veterinary drug residues in foods of animal origin.⁵ The 32nd Meeting of JECFA convened in 1987 in response to this recommendation and began the process of documenting the principles and policies followed by JECFA when executing its assigned work in this area.⁶ This meeting was specifically assigned to the evaluation of veterinary drug residues in foods and began the process of elaboration of

principles for the safety evaluation of veterinary drugs in food.⁶ This was the first meeting of JECFA where the drugs listed for evaluation were from a priority list provided by the CCRVDF, which held its inaugural meeting in 1985.

The Committee stated that in making recommendations it would consider principles contained in a document previously published by WHO on safety assessment of foods,⁷ principles applied in assessing veterinary drug residues at the 12th, 25th, 26th, and 27th Meetings of the Committee, and principles contained in the Expert Report.⁵ The Meeting Report provided definitions for “veterinary drug” and “residues of veterinary drugs” and detailed the information needed for these evaluations. This included information on a compound’s physico-chemical characteristics, veterinary use patterns, pharmacological characteristics, analytical methods, metabolism and pharmacokinetics, toxicological data, and residue depletion studies conducted under field conditions. The contents of this report provided the basis for the data currently requested and circulated prior to a JECFA meeting. In addition, the 32nd Meeting recorded the general principles that would be followed for assessment of these data.

Since 1987, typically every second meeting of JECFA has convened (with some exceptions) to deal with issues related to veterinary drug residues in foods, primarily on the request of the CCRVDF.

JECFA RELATIONSHIP TO CCRVDF

Recommendations for the establishment of maximum residue limits (MRLs) for residues of veterinary drugs in foods are made by the CCRVDF to the Codex Alimentarius Commission, which promulgates Codex standards. The scientific evaluation that leads to these recommendations is generated by JECFA. The essential difference in the roles of these organizations is that the risk assessment is performed by JECFA, while the risk management decisions are the responsibility of CCRVDF. The scientific evaluation conducted by JECFA for a veterinary drug will lead to the establishment of an Acceptable Daily Intake (ADI) and recommendations on MRLs. These are then submitted to the CCRVDF for consideration. The CCRVDF may elect either to accept the JECFA recommendations, with a recommendation that they progress in the Codex step process, or to return the compound to JECFA for further consideration.

CONSIDERATIONS USED BY JECFA TO DETERMINE ADIS AND MRLS

The 34th Meeting of JECFA defined several terms including MRL, total residues, extractable residues, nonextractable residues, bioavailable residues, and marker residue and began the process of describing how the nature of the residue

should be considered when establishing MRLs and estimating potential dietary intakes.⁸ The Committee also established the dietary intake factors used for estimating residue intake. These factors continued to be used up to the time of this review. These factors are daily intakes of 300 g of muscle tissue, 100 g of liver, 50 g of kidney, 50 g of fat, 100 g of egg, and 1.5 L of milk. At the time of the 34th Meeting, the MRLs were expressed on a wt/wt basis for all products except milk (for which the MRLs were expressed on a wt/vol basis). The units describing milk consumption were modified at the 52nd Meeting of JECFA (1999), thereby beginning the practice of expressing the milk intake as 1.5 kg. This enabled JECFA to establish MRLs for milk on a wt/wt basis, thereby making it comparable to that of other edible tissues.⁹

When establishing an ADI, the Committee considers all relevant information on the effects, including short-term and long-term effects (acute and chronic, carcinogenicity, genotoxicity, hormonal effects, reproductive effects, allergic response, and antimicrobial activity). Unless there is strong scientific evidence that the observed effect is relevant only to a particular test species and that there is not a potential risk to consumers, the effect that leads to the most conservative ADI is usually adopted. A decision to select the less conservative ADI is rare but may be taken when scientifically justified.

The Committee adheres to certain fundamental principles in establishing an ADI, the most basic being that an ADI will not be established unless the needed toxicological data are available to support the assessment. However, the Committee may establish a temporary ADI when it is confident that this can be done without posing a risk to consumers for the relatively short period of time required to generate the specific additional data requested for review.¹⁰ In such instances, a specific date is set by which the additional data must be submitted. Following review of these data, the Committee may establish a permanent ADI, continue the temporary ADI pending receipt of additional data, or decide not to extend the temporary ADI.

MRLs are only set when an ADI has been established. Only temporary MRLs are set for a temporary ADI. Temporary MRLs may also be set when a permanent ADI has been established if there are gaps in the depletion data or if the Committee is unable to identify a suitable analytical method for use in a regulatory program that monitors compliance with the MRLs. The MRLs are based on good veterinary practice. Therefore, they may not be set at the highest levels that could be established for an ADI. Consideration must also be given to other nonveterinary uses of a compound, particularly when compounds have horticultural uses and also uses for the treatment of parasites or other conditions of animals. Unless it is based on a unique toxicological concern that is not relevant for veterinary use, JECFA will use an ADI that

has been previously established by JMPR for horticultural purposes. In the case of abamectin, for example, the ADI established for horticultural use included the *delta*-8,9 isomer, which is formed following application to plants but is not formed during veterinary use.¹¹ In this case, a separate ADI was derived by JECFA for veterinary use.

A compound that can track the total residue, termed the marker residue, is selected. The marker residue is then used to set the MRL and the corresponding withdrawal time. An analytical method for tracking the levels of this residue in tissues is developed and must be validated. This marker residue, along with the validated analytical method, later serves as the basis of monitoring the presence of violative residues.

To establish MRLs, the Committee must account for the total residue and determine the fraction of the total residue tracked by the marker residue. The toxicological significance of all residues must be known, and any residue that cannot be definitively determined as being without toxicological concern is assumed to have the same toxicity as the parent compound or metabolite upon which the ADI is based. A correction factor that converts marker residue to total residue is established, with considerations given to the number of compounds that are of toxicological concern. The Theoretical Maximum Daily Intake (TMDI) is derived by multiplication of the MRL for each food used in the calculation (eg, muscle, liver, milk) by the dietary intake factor for that food and any correction factor that is required to adjust from marker residue to total residue. The calculated intake for all food items for which an MRL has been assigned is then summed and the total equals the TMDI, which should not exceed the ADI.

When temporary MRLs are established, it is with constraints, as in the case of temporary ADIs. The temporary MRL is established pending receipt of additional data by a date specified by JECFA. If the data are not received by that date, JECFA may grant an extension if there is reason to believe that the data will be provided within a reasonable time (for example, the work to generate the data is in progress). If this is not the case, the temporary MRLs may be withdrawn. Permanent MRLs will only be recommended by JECFA and accepted by CCRVDF when all required data have been received and evaluated.

CONSIDERATIONS USED BY JECFA TO DETERMINE ADIS AND MRLS: ANTIMICROBIAL COMPOUNDS

The 52nd Meeting of JECFA included a “decision tree” for establishing an ADI for drugs with antimicrobial activity. The first step is to assess the effects of the drug and its metabolites on the human intestinal flora and to determine if the ingested residues have antimicrobial properties. If they

do not have antimicrobial properties, then the toxicological effects are used to establish the ADI. Conversely, if the ingested residues do have antimicrobial properties, the next decision point is whether or not the residues will reach the lower bowel. If they will not, then, again, other toxicological considerations apply. If they will, the next consideration is whether or not the residues are inactivated in the bowel by either transformation or by irreversible binding to the intestinal contents. Again, if the residues are inactivated, then the toxicological effects become the focus of the determination. If the residues are not inactivated, the ADI derived from toxicological findings is assessed to determine whether or not it provides adequate protection to the gastrointestinal microflora. If it cannot be established that this is the case, the most sensitive effects on the human intestinal microflora are considered to establish an ADI. The upper limit of the ADI, which is usually expressed as a range from zero to some upper limit, is then derived using the following equation⁸:

$$ADI = \frac{MIC_{50}(\mu g / g) \times MCC(g)}{FA \times SF \times BW(kg)} \quad (1)$$

where ADI is the upper limit of acceptable daily intake of an antimicrobial agent, expressed in micrograms per kilogram of body weight; MIC₅₀ is the minimum concentration of the antimicrobial agent giving complete inhibition of growth of 50% of the cultures of the most relevant microorganism; MCC is equal to 220 g (representative mass of colonic content); FA is the fraction of oral dose available to act upon microorganisms in the colon; BW is body weight, expressed in kilograms (a value of 60 kg is used to represent a typical adult weight [mass]); and SF is the safety factor used to account for uncertainty about the amount and relevance of MIC data available for review.

The safety factor ranges from 1 to 10, depending on the uncertainty about the amount and relevance of the data available, with a factor of 1 being used when extensive amounts of relevant microbiological data are available. While the ADIs of most antimicrobial substances have been established on the basis of antimicrobial activity, there are cases where the decision has been based on toxicological concerns. For example, the ADI for penicillin is based on allergic response,¹⁰ while an ADI has not been established for chloramphenicol due to both a lack of data on carcinogenicity and to genotoxic concerns.¹²

CONSIDERATIONS USED BY JECFA TO DETERMINE ADIS AND MRLS: HORMONES

The no hormonal effect level has been used to establish the ADI for some xenobiotic growth promoters, such as zeranol¹⁶ and trenbolone acetate.⁸ The progestational effect in nonhuman primates, with a safety factor of 200, was used in estab-

lishing an ADI for megestrol acetate.¹³ General principles for the evaluation of endogenous hormonal substances were discussed at the 25th Meeting of JECFA, which concluded that it may be inappropriate to establish an ADI for a compound being assessed as a residue of a veterinary drug when it is also naturally present in the human body. On the basis of the existing safety assessments and in view of the difficulty in discriminating between endogenous versus exogenous hormones, the 32nd Meeting of JECFA concluded that an ADI should not be established for residues resulting from the growth-promoting use of estradiol, progesterone, and testosterone.⁶ The 52nd Meeting of the Committee, however, established ADIs for all 3 compounds based on studies that had become available subsequent to the earlier review. The Committee also noted that the levels of these hormones from animal-derived foods from treated animals were within the physiological range of the concentrations of these substances in cattle.⁹ It therefore did not establish MRLs but instead recommended that intake should be kept below the “excess intake levels” defined in the report.

THE CODEX STEP PROCESS FOR VETERINARY DRUGS

The 8-step Codex procedure for elaboration of a standard, which includes a detailed consultative and review process, is used to develop a Codex MRL for a veterinary drug residue in food. Step 1, the decision to begin the development of such a Codex standard, is taken when the CCRVDF determines that a compound is to be placed on its priority list for evaluation. Step 2 is the evaluation conducted by JECFA. Step 3 is the circulation of the JECFA evaluation and recommendations to members of the CCRVDF and to other interested international organizations. Step 4 is the consideration of the JECFA recommendations as a draft standard at a CCRVDF Meeting. At this point, one of several options may be pursued. The draft standard may be held at Step 4 pending further review or consideration by JECFA or CCRVDF. Alternatively, it may be forwarded to the Commission as a draft standard for further consideration. In other cases, it is advanced directly to Step 8 and forwarded to the Codex Commission for acceptance. However, in the typical situation, the draft standard is forwarded to the Commission at Step 5 and the Codex Secretariat circulates the draft standard to member states and to other interested international parties for another round of comment (Step 6). This is followed by the return of the draft standard and accompanying comments to CCRVDF (Step 7), where it undergoes further consideration prior to being forwarded to Step 8. The elaboration of a Codex MRL for a veterinary drug will typically take several years as the process moves from nomination to the priority list to initial JECFA review to consideration at 2 or more meetings of CCRVDF. Typically, CCRVDF meets at approx-

imately 18-month intervals, while JECFA has 1 meeting every 12 to 18 months to consider veterinary drugs. The process is designed to be deliberate and to provide adequate opportunity for questions and review before rendering a final decision on a standard. Additional requests for evaluation of a drug, such as new uses or formulations, follow the same path—nomination to the priority list, JECFA evaluation, review, comment, and recommendation as a draft standard within the CCRVDF.

SELECTION OF JECFA MEMBERS

Members of the JECFA are selected by the FAO and the WHO for their expertise and their independence. The members who review the available toxicological data and recommend an ADI for a veterinary drug residue in food are chosen by WHO. The members who evaluate the residue data and make the MRL recommendations are invited by FAO. The experts are chosen from rosters of qualified candidates that have been established by the FAO and WHO following a public call for nominations to these expert rosters. Since JECFA may convene to consider veterinary drugs, food additives, or contaminants, separate rosters of experts are maintained for these different areas. Currently, rosters are established for a 4-year period. Not all experts on a roster are invited for each meeting.

In general, every other meeting of JECFA is scheduled for evaluation of veterinary drug residues, but this is not a strict requirement. For example, the 54th and 58th Meetings of JECFA dealt with veterinary drug residues, the 55th Meeting dealt primarily with food additives, the 56th Meeting dealt with mycotoxins, and the 57th Meeting dealt with food additives and with chlorinated contaminants (eg, phenols, polychlorinated biphenyls, chlorinated dibenzofurans). The JECFA calendar is based on the needs and priorities of the Codex Committees to which it provides advice, as well as related emerging issues in food safety on which FAO and WHO may wish scientific advice.

Members of JECFA are invited as independent scientists, not as representatives of national governments or other organizations. Experts listed on the rosters from which members of the expert committees are drawn must not be associated with the regulated industry producing the products being evaluated. The experts are employed in government, academia, or as private consultants. Members must disclose any prior or existing relationships with the manufacturers of products under review in a written declaration prior to the Committee meeting. The members attending each meeting of the Committee are selected to provide the appropriate expertise and to provide global representation.

In addition to the “members,” each Committee includes scientists selected from a roster of experts designated as con-

sultants or temporary advisors. These individuals are listed as members of the Secretariat for the meeting. In practice, they execute duties similar to those of the members, preparing working papers and taking part in the discussions. Only members of the Committee and Secretariat are present during Committee sessions.

The nomination of a scientist from a government agency to a roster of experts requires agreement from the government that the individual can participate under the rules governing expert committees of FAO and WHO. This means that work done in preparation for and during the meeting is to reflect the individual scientific judgment of that scientist, not the policies of their government. The cost of meeting attendance, including travel, meals, and accommodations is paid for by the organization inviting the participant (FAO or WHO). Members are reimbursed for expenses but do not receive any other payment or honorarium for their services. Individuals invited to participate as members of the Committee or Secretariat receive a formal invitation in advance of the meeting.

JECFA PROCEDURES

The nomination of a compound by CCRVDF to the priority list for evaluation by JECFA requires that certain minimum criteria be met. The compound must be registered for veterinary use in a member state, the residues resulting from its use must have a potential to cause issues in trade, and there must be a sponsor who guarantees that a dossier will be provided for review when the evaluation is scheduled. A general call for data on each compound on the agenda for a JECFA meeting is posted on the FAO and WHO Web sites and is distributed to "governments, interested organizations, producers of the chemicals and individuals" with a submission date for data approximately 6 months prior to a scheduled meeting. The dossiers relating to residues and toxicology are submitted, respectively, to the FAO and WHO joint secretaries of the Committee. The joint secretaries then ensure that all information submitted for review is sent to the assigned reviewers for the preparation of expert reports. There is usually some duplication of material received by the WHO and the FAO, as both groups of reviewers receive information on the pharmacokinetics, metabolism, and distribution (as relevant to their considerations).

Data on a veterinary drug typically included in a toxicology submission include the following¹⁴:

- Reports of pharmacokinetic, metabolic, and pharmacodynamic studies in experimental and food producing animals.
- Equivalent studies in humans, if available.
- Studies on short-term and long-term toxicity, car-

cinogenicity, reproductive and developmental toxicity in experimental animals, and genotoxicity.

- Reports on any studies related to specific effects of the drug or its residues, such as mechanisms of toxicity, its no hormonal effect level, the induction of an immune response, or macromolecular binding.
- Studies of potential adverse effects on human gut flora for antimicrobial compounds.
- Studies on the use of and exposure to the drug by humans, such as occupational exposure or clinical use.

Data required for establishment of MRLs include the following¹⁴:

- Chemical identity and properties of the drug.
- Uses and recommended doses.
- Pharmacokinetic and metabolic studies in experimental and target animals (and in humans, if available).
- Residue depletion studies with radiolabeled drug in target animals, from zero withdrawal time to beyond the expected recommended withdrawal time, in an effort to provide information on total residues (free and bound) and major residue components. (This information is used to identify marker residues and target tissues.)
- Depletion studies with unlabeled drug using the appropriate formulations at concentrations up to maximum recommended dose in the target animal species and using the recommended route of application to provide information on depletion of marker residue in tissues of target animals, or in milk, eggs, or honey, as required.
- Analytical methods used in the studies to establish performance characteristics and validation status.
- A review of routine analytical methods, which may be appropriate for use by regulatory authorities for the detection of marker residues in target tissues.

The formal sponsor of a compound is the member state who nominates that compound for the priority list. In practice, the actual dossiers to be reviewed are usually provided by a product manufacturer, sometimes with additional information provided by member governments or other organizations. For purposes of this discussion, the term sponsor will be used to refer to the company or agency that provides a dossier for JECFA review. The typical dossier would contain the same studies submitted to national or regional regulatory authorities to obtain an approval for use of a veterinary drug within that jurisdiction. In some cases, there may be multiple manufacturers of products containing a drug, particularly for

those for which the patent has expired. Different product formulations may be submitted at different times for review. Alternatively, dossiers may be provided for the same meeting by several “sponsors.” When a second sponsor requests a reevaluation of a compound that has been previously reviewed, an attempt is made by the Secretariat to inform the original sponsor to provide them with an opportunity to comment on any issues that may arise during the new review. Contacts between sponsors and experts are through the Secretariat.

In a typical review, the dossier for a compound is sent to at least 2 reviewers each for toxicology and for residues, respectively, prior to a JECFA Meeting. These reviewers are responsible for drafting the monographs reviewing the toxicology and residue issues, as well as a working draft of the summary report on the compound for inclusion in the meeting proceedings. The reviewers may divide the work between them, so that each person drafts a portion of the monograph. Alternatively, one person may draft the monograph, while the other reviews it for completeness and accuracy. During the monograph preparation, questions may be forwarded to the sponsor via the Secretariat to clarify any apparent errors, discrepancies, or omissions in the dossier. The reviewers may also independently review the scientific literature for additional information not included in the dossier. Once the assigned reviewers are satisfied with the draft, it is forwarded to the Secretariat and then distributed to the members of the Committee, including the invited temporary advisors and consultants. Using the material in the monographs, the reviewers draft summary documents for inclusion in the meeting summary report, covering the important issues from the toxicology and residue monographs related to the expected decisions on the compound.

A typical JECFA Meeting extends over a 2-week period, beginning on a Tuesday morning and finishing the following Thursday. Committee members will schedule a session on the weekend, if required, or may opt to work individually or in small groups on specific compounds or general issues. The meeting begins with a joint opening session to introduce the members, elect a chair for the Meeting, and establish an agenda and working arrangements, following which the FAO and WHO experts separate and choose chairs and rapporteurs for their respective groups. Meetings alternate between the headquarters of the WHO in Geneva and the FAO in Rome. Traditionally, when the meeting is at the WHO, a member invited by WHO serves as Committee chair, whereas a member invited by FAO is elected chair for meetings held at the FAO.

During the first day of a meeting, the assigned experts give a brief presentation on the key issues related to their assignments, after which the Committee members begin the process of review and discussion. For the WHO experts, the

major objective is to determine if an ADI can be established for each substance under review based on the information provided, while the focus for the FAO experts is to determine appropriate MRLs when an ADI has been established and to identify suitable methods of analysis that can be used to determine compliance with the proposed MRLs. The source documents used for these discussions are the dossiers, the draft monographs, and the draft summaries. The monographs and summaries are revised and updated by the designated reviewers as the discussion proceeds. Working parties may be assigned to particular issues that arise from the discussion and that require additional information or evaluation. Key issues that may require additional information are identified, and questions are drafted to send to sponsors by Thursday or Friday of the opening week of the meeting. Sponsors may reply in writing or may meet with the Committee in a special open session to provide responses to the questions.

The special open session is usually held on Monday of “week 2” of the meeting. The Committee is not formally in session during this period, as Committee sessions are closed to outsiders. According to procedures, the sponsor provides a response to questions sent in the previous week, giving as much detail as possible. While follow-up questions may result from the additional information provided with the response, it is not considered appropriate to raise new issues at this session. Only matters related to the questions previously sent to the sponsor are to be discussed. This applies equally to the sponsor, whose representatives are to limit their comments to those same questions.

Following completion of the meeting with the sponsors, the Committee reconvenes in a formal closed session to continue deliberations, begin finalizing decisions on each compound, and begin assembling the report. Each draft of the summary is reviewed by all Committee members to ensure that all are in agreement with the stated facts, the data interpretations, the scientific basis for decisions, and the decisions themselves. Care is taken to identify discrepancies or information gaps and to include in the report any requests for further studies to address these issues before final recommendations are made.

A JECFA Meeting not only deals with substances on the agenda but also frequently deals with issues of Committee policy, the procedure for developing text for the report, and the creation of monographs explaining the scientific basis for certain procedures and policies. Other issues that may be addressed at the request of the Secretariat or the CCRVDF include the harmonization of issues involving other committees or comments on documents under consideration by the CCRVDF. The JECFA process is dynamic, with the procedures and policies frequently being reviewed and modified to reflect current best practices in toxicological evaluation and residue chemistry.

JECFA PUBLICATIONS

Each meeting of JECFA to review veterinary drug residues in foods produces 3 scientific reports: the report of the Committee, which includes the key factors considered and the recommendations published in the WHO Technical Report Series; the compilation of residue monographs published in the FAO Food and Nutrition Paper Series 41/X; and the compiled toxicological monographs published in the WHO Food Additive Series. The toxicological and residue reviews contain summaries of many studies that have not been published in the open scientific literature. Therefore, they can serve as valuable resources both for scientists planning further research on the drugs and for regulatory officials. The key elements of the transparency of the process include these publications and the various documents published on the Web sites of Codex Alimentarius and JECFA. The policies and procedures followed by JECFA in conducting assessments have been carefully documented in the meeting reports and are available for public scrutiny.

The review processes used by JECFA are dynamic and constantly under review and revision to reflect current best scientific practices. The Secretariat and the members of the Committee carefully guard the independence and the scientific integrity of the process.

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