

**UNITED STATES – CONTINUED SUSPENSION OF
OBLIGATIONS IN THE EC – HORMONES DISPUTE**

Report of the Panel

Addendum

This addendum contains Annex E to the Report of the Panel to be found in document WT/DS320/R. The other annexes can be found in the following addenda:

- Annex A: Add.1
- Annex B: Add.2
- Annex C: Add.3
- Annex D: Add.4
- Annex F: Add.6
- Annex G: Add.7

ANNEX E

**REPLIES OF THE CODEX ALIMENTARIUS COMMISSION,
THE JOINT FAO/WHO JECFA SECRETARIAT AND
THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
TO CERTAIN QUESTIONS POSED BY THE PANEL
TO INTERNATIONAL ORGANIZATIONS**

Contents		Page
Annex E-1	Replies of the Codex Alimentarius Commission to certain questions posed by the Panel to international organizations	E-2
Annex E-2	Replies of the Joint FAO/WHO JECFA Secretariat to certain questions posed by the Panel to international organizations	E-104
Annex E-3	Replies of the International Agency for Research on Cancer to certain questions posed by the Panel to international organizations	E-127

ANNEX E-1

REPLIES OF THE CODEX ALIMENTARIUS COMMISSION TO CERTAIN QUESTIONS POSED BY THE PANEL TO INTERNATIONAL ORGANIZATIONS

1. Please briefly describe the procedure for the elaboration and adoption of an international standard by Codex. What is the decision-making process for the adoption of an international standard?

The procedure for the elaboration and adoption of Codex standards and related texts are published in the *Procedural Manual of the Codex Alimentarius Commission* (see Annex 1). The Procedure for the Elaboration of Codex Standards was comprehensively revised in 1993 to provide a uniform elaboration procedure for all Codex standards and related texts, including maximum residue limits (consisting of 8 Steps under the normal procedure and 5 Steps under the accelerated procedure). The revised uniform elaboration procedure superseded the separate procedure for the elaboration of Codex Maximum Residue Limits (MRLs) for Veterinary Drugs.¹ The Procedure was further revised in 2004 to introduce the strategic planning process and the critical review of new work proposals at Step 8.

In essence the *8-step procedure* followed in the development and approval of the standard involves:

Prior to Step 1: The *submission of a proposal* for a new standard or related text by a national government or a subsidiary body of the Commission. This is usually accompanied by a project document that indicates the purpose, scope and proposed timeline time frame for the new work. The project document is reviewed by the Executive Committee, which forward its opinion to the Commission (this process is called "critical review").

In the case of MRLs for veterinary drugs, submission of project documents is not required; instead, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) prepares a priority list of veterinary drugs requiring evaluation or re-evaluation by JECFA, which is submitted to the Commission for approval.

Step 1 a *decision by the Commission that a standard be developed* as proposed. "Criteria for the Establishment of Work Priorities" exist to assist the Commission in its decision-making and in selecting the subsidiary body to be responsible for steering the standard through its development. If necessary, a new subsidiary body – usually a specialized task force - may be created. In the case of matters related to the residues of veterinary drugs, CCRVDF always undertakes the standards development work assigned by the Commission in accordance with its terms of reference (Annex 2);

Step 2 the preparation of a proposed draft standard;

¹ Elaborated by the CCRVDF and adopted by the 18th Session of the Codex Alimentarius Commission (1989) (ALINORM 89/40 para. 215). The 8-step procedure, involved: Steps 1, 2 and 3: the distribution of the draft recommendations for MRLs for veterinary drugs, based on JECFA evaluations and request comments from Government and interested organisation; Step 4: examination by the CCRVDF in the light of the comments. The CCRVDF, when formulating its recommendations for proposed draft MRLs, takes all appropriate matters into consideration including the need for urgency, the government comments at Step 3 and the likelihood of new evidence becoming available in the immediate future and, on the basis of such considerations, indicates to the Commission those proposed draft MRLs which, in its view, need to be passed through the full Procedure and those for which there might be an omission of Step 6 and 7; Steps 5-8: as for the Procedure for the Elaboration of world-wide standards.

<u>Step 3</u>	the circulation of the proposed draft standard for governments' and interested organizations' comments; in the case of MRLs for veterinary drugs, the recommendations of JECFA are circulated for comments at this Step;
<u>Step 4</u>	the discussion at Committee level;
<u>Step 5</u>	the submission of the proposed draft standard to the Commission for adoption as draft standard ("preliminary adoption");
<u>Step 6</u>	the circulation of the draft standard for governments' and interested organizations' comments;
<u>Step 7</u>	the discussion at Committee level;
<u>Step 8</u>	the submission of the draft standard to the Commission for adoption as Codex standard.

More details of the Elaboration Procedure are given in Annex 1.

A Committee may decide to submit a text to the Commission for adoption at Step 5 and 8, with the omission of Steps 6 and 7. The Commission may also approve the use of an *accelerated* procedure for the elaboration of these standards, using a 5-step elaboration process.

The Commission may also decide to return a proposed draft or a draft standard from Step 5 or 8 to a previous step when it considers that more discussion is necessary at the Committee level.

The procedure for revision of Codex standards and related texts follows that used for the elaboration of standards. The Commission and its subsidiary bodies are committed to the revision of Codex standards and related texts as necessary to ensure they are consistent with and reflect current scientific knowledge. Each member of the Commission is responsible for identifying and presenting to the appropriate committee any new scientific and other relevant information that may warrant revision of existing Codex standards or related texts.

The *Procedure for the Elaboration of Codex Standards and Related Texts* allows for full discussion and exchange of views on the issue under consideration, in order to ensure the transparency of the process and, if necessary, arrive at compromises that would facilitate consensus. Written comments from governments and observers are solicited at Steps 3, 5, 6 and 8; furthermore, governments and observers can present their positions directly in a committee meeting and exchange views with other delegations at Steps 4 and 7.

The Commission attaches a great importance of achieving consensus at all stages of the elaboration of standards and that draft standards should, as a matter of principle, be submitted to the Commission for adoption only where consensus has been achieved at the technical level. For this purpose, the Commission at its 26th Session (2003) adopted "Measures to Facilitate Consensus" for inclusion in the Procedural Manual (see Annex 3).

2. Please briefly explain the differences between Codex standards, codes of practice, guidelines, principles and other recommendations.

The texts developed by the Codex Alimentarius Commission may be divided in two main groups: i) texts intended for use by Governments and are published in the Codex Alimentarius (these include Codex standards, codes of practice, guidelines, principles and other recommendations); and ii) texts

intended to guide the work of the Commission and its subsidiary bodies and are included in the Procedural Manual (these include the Statutes and Rules of Procedure of the Commission, other procedures, guidelines, principles and other recommendations.)

Codex standards usually relate to product characteristics and may deal with all government-regulated characteristics appropriate to the commodity, or only one characteristic. Maximum residue limits (MRLs) for residues of veterinary drugs in foods are examples of standards dealing with only one characteristic (i.e. numerically expressed limits of a chemical substance in a given food (animal tissue or milk)). There are *Codex general standards* for food additives and contaminants and toxins in foods that contain both general and commodity-specific provisions. The Codex General Standard for the Labelling of Prepackaged Foods covers all foods in this category. Codex commodity standards, on the other hand, include provisions on the product definition, essential quality factors, labelling and health-related aspects for a given product or a group of products. Because standards relate to product characteristics, they can be applied wherever the products are traded. *Codex methods of analysis and sampling*, including those for contaminants and residues of pesticides and veterinary drugs in foods, are also considered Codex standards.

Codex codes of practice (including codes of hygienic practice) define the production, processing, manufacturing, transport and storage practices for individual foods or groups of foods that are considered essential to ensure the safety and suitability of food for consumption. For food hygiene, the basic text is the Codex General Principles of Food Hygiene, which recommends the use of the Hazard Analysis and Critical Control Point (HACCP) food safety management system. The Codex Code of Practice on the Control of the Use of Veterinary Drugs provides general guidance in relation to the use of veterinary drugs in food production.

Codex guidelines fall into two categories: i) principles that set out policy in certain key areas; and ii) guidelines for the interpretation of these principles or for the interpretation and/or application of the provisions of the Codex general standards.

Codex guidelines include those for food labelling, especially the regulation of claims made on the label. This group includes guidelines for nutrition and health claims; conditions for production, marketing and labelling of organic foods; and foods claimed to be "halal". There are several guidelines that interpret the provisions of the Codex Principles for Food Import and Export Inspection and Certification, and guidelines on the conduct of safety assessments of foods from DNA-modified plants and micro-organisms.

The status of Codex standards and related texts within the Codex system and in the international framework has changed several times since the Commission was established in 1962.

These changes can be identified in four periods: until 1981; from 1981 to 1995; from 1995 to 2006; and since 2006 when Codex Acceptance Procedures were formally abolished.

Until 1981 – The elaboration of a worldwide standard consisted of 11 Steps until the Steps beyond Step 8 were eliminated in the 5th Edition of the Procedural Manual. The eliminated Steps were: Step 9 (the "recommended standard" is sent to FAO/WHO members for acceptance, and the latter notify their acceptance); Step 10 (the Secretariat periodically publishes notifications received on the recommended standard); Step 11 (the "recommended standard" is published as a "Codex standard" when the Commission determines that it is appropriate to do so in the light of notifications received).

From 1981 to 1995 – Codex Standards and Related Texts had habitually been classified on the basis of whether or not texts are intended to be subject to the Acceptance Procedures laid down in paragraphs 4, 5 and 6 of the General Principles of the Codex Alimentarius (see Procedural Manuals prior to the 15th Edition; e.g. Annex 4). Those adopted texts subjected to the Acceptance Procedures

were termed "mandatory" and the other texts "advisory". The term "mandatory" did not mean that members were under obligations to accept Codex standards as were. Members could choose among three different forms of acceptance: "Full Acceptance"; "Acceptance with specified deviations"; and "Free distribution"², in accordance with their own legal and administrative procedures. The situation was different regarding the acceptance of Codex Maximum Limits for Residues of Pesticides and Veterinary Drugs in Food. In this case, the General Principles of the Codex Alimentarius only provided the possibility of Full Acceptance or Free Distribution (see section 6, Annex 4).

Prior to the establishment of the WTO in 1995 and the entry in force of the WTO Agreements on the Application of Sanitary and Phytosanitary (SPS) Measures and on Technical Barrier to Trade (TBT), the status of Codex standards was defined only within the Codex system; in particular they had no direct binding effect on member countries per se. Countries were undertaking specific obligations only when they declared acceptance according to one of the modalities indicated in section 4A, 5A and 6A of the General Principles of the Codex Alimentarius (Annex 4). In particular, a country had the obligation to accept a product for distribution on its territory only when it has declared acceptance.

The notifications of acceptance received in the Codex Secretariat became increasingly rare by the end of 1980s, because many countries ceased to implement a national procedure for the acceptance of standards. The Progress Report on Acceptances was a standing item in the agenda of the Commission since its early years but was discontinued after 1993, and was replaced by a discussion on the usefulness of acceptances in the light of the WTO Agreements. Acceptances were published in 1989 for standards and in 1983 for pesticide residues for the last time. Notifications became very rare in the 1990s.

From 1995 to 2006 - Codex standards and related texts started to enjoy a new status in the framework of WTO Agreements. In regard to the differences between standards, guidelines and other recommendations, It is worth noting the clarification provided by the WTO SPS Committee in March 1998 in response to the query sent from Codex: the SPS Committee responded that the provisions of the SPS Agreement did not differentiate between the three terms "standards", "guidelines" or "recommendations" (see Annex 5).

Meanwhile, the 22nd Session of the Codex Alimentarius Commission (1997) agreed that the use of the terms "mandatory" and "advisory" was confusing and not consistent with the provisions of the SPS and TBT Agreements, and stated that they should no longer be used.³ Once standards and related texts have been adopted by the Codex Alimentarius Commission, they are recognized as a reference under the SPS Agreement in matters of food safety and under TBT for other technical matters relevant to food regulation.

After 2006 (abolition of Codex Acceptance Procedures)

The 28th Session of the Codex Alimentarius Commission (2005) agreed to abolish the acceptance procedures and amend relevant section of the Procedural Manual accordingly.⁴ As stated above, the Codex acceptance procedure covered only Codex Standards (Commodity or General) and Maximum Residue Limits, and did not cover other texts adopted by the Commission, such as codes of practice and other recommendations. As a consequence of abolishing acceptance procedure, the dichotomy between "standards and MRLs" and "other texts" within the Codex Alimentarius was removed, resulting in a uniform status of all Codex standards and related texts.

² "Free Distribution" was introduced as a new category of acceptance in 1989 by the 18th Session of the Commission.

³ ALINORM 97/37, para. 171.

⁴ ALINORM 05/28/41, para. 36.

3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

The Codex Alimentarius Commission initiated work to incorporate risk assessment principles into Codex decision-making and procedures on the basis of the Joint FAO/WHO Conference on Food Standards, Chemicals in Food and Food Trade, held in Rome in 1991. The Commission, at its 19th and 20th Session agreed on the incorporation of risk assessment principles in its procedure. To assist the Commission, FAO and WHO convened a joint FAO/WHO expert consultation on the application of risk analysis to food standards issues in 1995.

The *Statements of principles relating to the role of food safety risk assessment*⁵, adopted by the 22nd Session of the Codex Alimentarius Commission (1997), state that:

1. *Health and safety aspects of Codex decisions and recommendations should be based on a risk assessment, as appropriate to the circumstances.*
2. *Food safety risk assessment should be soundly based on science, should incorporate the four steps of the risk assessment process, and should be documented in a transparent manner.*
3. *There should be a functional separation of risk assessment and risk management, while recognizing that some interactions are essential for a pragmatic approach.*
4. *Risk assessment should use available quantitative information to the greatest extent possible and risk characterizations should be presented in a readily understandable and useful form.*

The 22nd Session of the Commission also adopted an Action Plan for Codex-wide Development and Application of Risk Analysis Principles and Guidelines. In accordance with the Plan and on the basis of the preparatory work by the Codex Committee on General Principles, the 26th Session of the Codex Alimentarius Commission (2003) adopted the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius* for inclusion in the Procedural Manual⁶ (see Annex 6). The objective of the Principles is to provide guidance to Codex subsidiary bodies and FAO/WHO expert bodies and consultations, so that food safety and health aspects of Codex standards and related texts are based on risk analysis. The Principles clearly define the responsibilities of the Commission and its subsidiary bodies for risk management decision and of the joint FAO/WHO expert bodies and consultation for risk assessment.

Following the adoption of the Working Principles, the Commission requested that relevant Codex Committees develop or complete specific guidelines on risk analysis in their respective areas for inclusion in the Procedural Manual. The Commission noted that these texts would be submitted to the Committee on General Principles in order to ensure coordination of work and consistency with the overarching Working Principles.⁷ At the same time, the Committee on General Principles pursued elaboration of risk analysis guidance for use by governments (this work is still ongoing).

Within the framework of the above request by the Commission, the 16th Session of the CCRVDF (2006) completed work on: "Risk Analysis Principles applied by the Codex Committee on Residues

⁵ Procedural Manual of the Codex Alimentarius Commission (15th Edition).

⁶ ALINORM 03/41, para. 146 and Appendix IV.

⁷ ALINORM 03/41, para. 147.

of Veterinary Drugs in Foods" and "Risk Assessment Policy for the Setting of MRLs in Food" and forwarded these to the Codex Alimentarius Commission.⁸ The two documents will be considered by the 30th Session of the Codex Alimentarius Commission in 2007 (after review by the Codex Committee on General Principles) for adoption and inclusion in the Procedural Manual.

The Principles define the responsibilities of the various parties involved: the responsibility for providing advice on risk management concerning residues of veterinary drugs lies with the Codex Alimentarius Commission (CAC) and its subsidiary body, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRDVF), while the responsibility for risk assessment lies primarily with the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

The Risk Assessment Policy applies to the work of JECFA in the context of Codex and in particular as it relates to advice requests from CCRVDF.

4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)]

There is no adopted Codex standard or related text on the risk assessment of residues on veterinary drugs that provides guidance to governments. However, at the request of 23rd session of the Commission, the CCRVDF in 2000 started develop texts on risk analysis principles in the work of the Committee. The 16th Session of the Committee completed work on two texts: Risk Analysis Principles applied by the Codex Committee on Residues of Veterinary Drugs in Foods and Risk Assessment Policy for the Setting of MRLs in Food, for inclusion in the Procedural Manual (see the answer to Question 3, above). The documents may be adopted by the Commission in 2007. Annex 7 describes relevant discussion in CCRVDF to strengthen science-based approach to risk analysis into its work.

As other internal documents on risk analysis, Codex has already adopted Risk Analysis Principles Applied by the Codex Committee on Food Additives and Contaminants and CCFAC Policy for Exposure Assessment of Contaminants and Toxins in Foods and Food Groups; the Commission will possibly adopt Risk Analysis Principles Applied by the Codex Committee on Pesticides Residues, finalized by the 38th Session of the CCPR (2006) in 2007.

As the adopted texts on risk analysis providing guidance to governments, Codex has: Principles and Guidelines for the Conduct of Microbiological Risk Assessment (CAC/GL 30-1999); and Principles for the Risk Analysis of Foods Derived from Modern Biotechnology (CAC/GL 44-2003) and two accompanying guidelines for food safety assessment of foods derived from recombinant-DNA plants and microorganisms (CAC/GL 45-2003; CAC/GL 46-2003).

In addition, the Codex Committee on Food Hygiene (CCFH) is currently developing Principles and Guidelines for the Conduct of Microbiological Risk Management (at Step 6) and the *ad hoc* Codex Intergovernmental Task Force on Biotechnology is working on Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals.

5. Please briefly describe the three components of a risk analysis exercise (risk assessment, risk management and risk communication) as defined by Codex and explain how they differ.

⁸ ALINORM 06/29/31 para. 111 and Appendices VIII and IX.

Definitions of Risk Analysis Terms related to Food Safety were adopted by the 22nd Session of the Codex Alimentarius Commission⁹ (1997) and were included in the Procedural Manual (see Annex 8). The definitions of "Risk Management" and "Risk Communication" were revised by the 23rd Session of the Codex Alimentarius Commission (1999)¹⁰ in the light of the reports of the Joint FAO/WHO Experts Consultations on Risk Management and Food Safety and on Risk Communication in Relation to Food Standards and Safety Matters. The *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius* describe the three components of risk analysis in more detail (see Annex 6).

The Procedural Manual of the Codex Alimentarius Commission provides the following definitions (*in italics*):

Risk Assessment: *A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization*¹¹

Risk Management: *The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.*¹¹

Risk Communication: *The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.*¹¹

6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

The Procedural Manual of the Codex Alimentarius Commission provides the following definitions (*in italics*):

Hazard identification. *The identification of biological, chemical and physical agents capable of causing adverse health effects and which may be present in food.*¹¹

Hazard characterization. *The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are obtainable.*¹¹

Exposure assessment. *The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant.*¹¹

Risk characterization. *The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.*¹¹

⁹ ALINORM 97/37, para. 31 and Appendix II.

¹⁰ ALINORM 99/37, para. 70 and Appendix IV.

¹¹ Procedural Manual of the Codex Alimentarius Commission (15th Edition).

9. Please provide definitions for the following terms: Acceptable Daily Intake (ADI) and Maximum Residue Limit (MRL).

A definition for *Codex Maximum Limits of Residues of Veterinary Drugs* (MRLVD) is contained in the Procedural Manual of the Codex Alimentarius Commission (see below). A definition for *Acceptable Daily Intake* (ADI) is included in the "Glossary of Terms and Definition" (CAC/MISC 5 1993) (see below), which has been elaborated by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) with a view of providing information and guidance to the Committee, and it is intended for internal Codex use only.¹²

***Codex Maximum Residue Limit for Veterinary Drugs (MRLVD)** is the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food.*

It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects.

When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available.¹¹

***Acceptable Daily Intake (ADI):** An estimate by JECFA of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard man = 60 kg) (Note - definition previously established and adopted by the JECFA, which has been modified by the Codex Committee on Veterinary Drugs in Foods).¹³*

12. In para. 129 and 168 of its Replies to the Panel's questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not." Does Codex have risk management options other than (1) the establishment of an MRL, (2) the establishment that an MRL is not necessary, or (3) no recommendation?

The Terms of Reference of the CCRVDF also include the development of codes of practice (Annex 2). The development of a Code of Practice might therefore be considered by the Committee as a possible option to manage risks related to residues of veterinary drugs.

The CCRVDF, at its 16th Session, agreed to the preparation of a discussion paper to identify risk management issues to be addressed by the Committee and re-established the Working Group on Substance with no ADI/MRL in order to, *inter alia*, consider management option for compound to be evaluated by JECFA where a management decision is pending.¹⁴

¹² Please note that Codex does not adopt ADI. JECFA MRLs and ADI are separate outputs of the risk assessment process and only JECFA recommendations for MRLs are considered by the Codex process.

¹³ Glossary of Terms and Definition" (CAC/MISC 5-1993).

¹⁴ ALINORM 06/29/31 paras 113 and 134.

15. Please provide the definition of the term Good Veterinary Practice (GVP). Are there any relevant Codex standards, guidelines, or recommendations relating to GVP?

There is no a Codex definition of the term Good Veterinary Practice (GVP). Codex has developed a definition of the term ***Good Practice in the Use of Veterinary Drug (GPVD)***, which is contained in the Procedural Manual of the Codex Alimentarius Commission (see below).

*Good Practice in the Use of Veterinary Drugs (GPVD) is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions.*¹²

Relevant texts related to GPVD include:

- The recommended international "*Code of Practice for the Control of the Use of Veterinary Drugs*" (CAC/RCP 38-1993) sets out guidelines on the prescription, application, distribution and control of drugs used for treating animals, preserving animal health or improving animal production (see Annex 9);
- *Codex Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods* (CAC/GL 16-1993) (see Annex 10). Please Note that CCRVDF is currently working on a revision of the Guidelines (the 16th Session of CCRVDF has forwarded a proposed draft of the Guidelines to the 29th Session of the Codex Alimentarius Commission for preliminary adoption at Step 5).¹⁵

16. Please provide an update on the status of international standards with respect to the six hormones at issue. What are the remaining procedures before the adoption of a standard on melengestrol acetate (MGA)? What is the timeframe for their completion?

Oestradiol-17 β – MRL adopted by the 21st Session of the Codex Alimentarius Commission (1995); no more considered since the 12th CCRVDF (2000);

Progesterone – MRL adopted by the 21st Session of the Codex Alimentarius Commission (1995); no more considered since the 12th CCRVDF (2000);

Testosterone – MRL adopted by the 21st Session of the Codex Alimentarius Commission (1995); no more considered since the 12th CCRVDF (2000);

Trenbolone acetate - MRL adopted by the 21st Session of the Codex Alimentarius Commission (1995); no more considered since 7th CCRVDF (1992);

Zeranol - MRL adopted by the 21st Session of the Codex Alimentarius Commission (1995); no more considered since 7th CCRVDF (1992);

Melengestrol acetate – Currently under consideration by CCRVDF. Annex 11 provides a chronological history of the CCRVDF consideration of MGA.

18. What happens if new evidence or studies throw into doubt a Codex standard? What are the procedures for incorporating more recent developments into Codex work? Has the European Communities approached Codex for this purpose with respect to the hormones at issue in this case?

¹⁵ ALINORM 06/29/31, para. 86 and Appendix VII.

According to the *Procedure of the Elaboration of Codex Standard and Related Texts*, it will be for the Commission itself to keep under review the revision of "Codex standards" (see Annex 1, para. 8) and instruct Codex subsidiary bodies to undertake this work. Proposals for new work, including the revision of Codex Standards, are also submitted to the Commission by a Codex subsidiary body or a Codex Member.

In the case of estradiol-17 beta, progesterone and testosterone, they were re-evaluated by the 52nd JECFA (1999) at the initiative of the JECFA Secretariat. The 12th CCRVDF (2000), in recognising that it had not requested the re-evaluation of the three substances and that the new MRLs recommended by the 52nd JECFA did not differ significantly from the current MRLs, decided to not consider the new recommendation of the 52nd JECFA.¹⁶

In the case of MGA, the 58th JECFA has re-evaluated MGA at the request of the 14th CCRVDF on the basis of new information and additional data to be submitted.¹⁷ During the discussion on MGA at the 16th CCRVDF, there was no request for a further re-evaluation of MGA.¹⁸

¹⁶ ALINORM 01/31, para. 84.

¹⁷ ALINORM 99/213/31, para 113 and Appendix VII.

¹⁸ ALINORM 06/29/31, para. 69.

List of Annexes

	<u>Page</u>
Annex 1 <i>Procedures for the Elaboration of Codex Standards and Related Texts</i> (Procedural Manual of the Codex Alimentarius Commission, 15 th Edition)	E-14
Annex 2 Terms of reference and meetings records of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF)	E-23
Annex 3 <i>Measures to Facilitate Consensus</i> (Procedural Manual of the Codex Alimentarius Commission, 15 th Edition)	E-24
Annex 4 <i>General Principles of the Codex Alimentarius and Guidelines for the Acceptance Procedure for Codex Standards</i> (Procedural Manual of the Codex Alimentarius Commission, 14 th Edition)	E-25
Annex 5 SPS Committee's clarification "how the Committee would differentiate standards, guidelines or recommendations in relation to the implementation of the SPS Agreement"	E-34
Annex 6 <i>Codex Working Principles for Risk Analysis Application in the Framework of the Codex Alimentarius</i> (Procedural Manual of the Codex Alimentarius Commission, 15 th Edition)	E-36
Annex 7 Consideration of risk analysis in CCRVDF (history)	E-41
Annex 8 Definitions of Risk Analysis Terms Related to Food Safety (Procedural Manual of the Codex Alimentarius Commission, 15 th Edition)	E-56
Annex 9 Recommended International <i>Code of Practice for the Control of the Use of Veterinary Drugs</i> (CAC/RCP 38-1993)	E-58
Annex 10 <i>Codex Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods</i> (CAC/GL 16-1993)	E-62
Annex 11 Melengestrol acetate – CCRVDF chronology	E-103

Other References:

Reports of the past sessions (1st to 16th) of the Codex Committee on Residues of Veterinary Drugs in Foods

WHO 1995. *Application of Risk Analysis to Food Standards Issues*. Report of the Joint FAO/WHO Expert Consultation. Geneva, Switzerland, 13-17 March 1995. WHO/FNU/FOS/95.3

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FAO/WHO. 2006 (in preparation). *The use of microbiological risk assessment outputs to develop practical risk management strategies*. Report of a joint FAO/WHO meeting, Kiel, Germany, 3-7 April, 2006.

ANNEX 1

PROCEDURES FOR THE ELABORATION OF CODEX STANDARDS AND RELATED TEXTS¹

Note: These procedures apply to the elaboration of Codex standards and related texts (e.g, codes of practice, guidelines) adopted by the Codex Alimentarius Commission as recommendations for governments.

INTRODUCTION

The full procedure for the elaboration of Codex standards is as follows.

1. The Commission shall implement a unified approach in the area of standards development by taking its decisions, based on a strategic planning process ("standards management") (See Part 1 of this document).
2. An on-going critical review shall ensure that proposals for new work and draft standards submitted to the Commission for adoption continue to meet the strategic priorities of the Commission and can be developed within a reasonable period of time, taking into account the requirements and availability of scientific expert advice (See Part 2 of this document).
3. The Commission decides, taking into account the outcome of the on-going critical review conducted by the Executive Committee, that a standard should be elaborated and also which subsidiary body or other body should undertake the work. Decisions to elaborate standards may also be taken by subsidiary bodies of the Commission in accordance with the above-mentioned outcome subject to subsequent approval by the Commission at the earliest possible opportunity. The Secretariat arranges for the preparation of a "proposed draft standard" which is circulated to governments for comments and is then considered in the light of these by the subsidiary body concerned which may present the text to the Commission as a "draft standard". If the Commission adopts the "draft standard" it is sent to governments for further comments and in the light of these and after further consideration by the subsidiary body concerned, the Commission reconsiders the draft and may adopt it as a "Codex standard". The procedure is described in Part 3 of this document.
4. The Commission or any subsidiary body, subject to the confirmation of the Commission may decide that the urgency of elaborating a Codex standard is such that an accelerated elaboration procedure should be followed. While taking this decision, all appropriate matters shall be taken into consideration, including the likelihood of new scientific information becoming available in the immediate future. The accelerated elaboration procedure is described in Part 4 of this document.
5. The Commission or the subsidiary body or other body concerned may decide that the draft be returned for further work at any appropriate previous Step in the Procedure. The Commission may also decide that the draft be held at Step 8.
6. The Commission may authorise, on the basis of two-thirds majority of votes cast, the omission of Steps 6 and 7, where such an omission is recommended by the Codex Committee entrusted with the elaboration of the draft. Recommendations to omit steps shall be notified to Members and interested international organizations as soon as possible after the session of the Codex Committee concerned. When formulating recommendations to omit Steps 6 and 7, Codex Committees shall take all appropriate matters into consideration, including the need for urgency, and the likelihood of new scientific information becoming available in the immediate future.

¹ Procedural Manual of the Codex Alimentarius Commission (15th Edition).

7. The Commission may at any stage in the elaboration of a standard entrust any of the remaining Steps to a Codex Committee or other body different from that to which it was previously entrusted.

8. It will be for the Commission itself to keep under review the revision of "Codex standards". The procedure for revision should, *mutatis mutandis*, be that laid down for the elaboration of Codex standards, except that the Commission may decide to omit any other step or steps of that Procedure where, in its opinion, an amendment proposed by a Codex Committee is either of an editorial nature or of a substantive nature but consequential to provisions in similar standards adopted by the Commission at Step 8.

9. Codex standards and related texts are published and are sent to governments as well as to international organizations to which competence in the matter has been transferred by their Member States (see Part 5 of this document).

PART 1. STRATEGIC PLANNING PROCESS

1. Taking into account the "*Criteria for the Establishment of Work Priorities*", the strategic plan shall state broad priorities against which individual proposals for standards (and revision of standards) can be evaluated during the critical review process.

2. The strategic plan shall cover a six-year period and shall be renewed every two years on a rolling basis.

PART 2. CRITICAL REVIEW

Proposals to Undertake New Work or to Revise a Standard

1. Prior to approval for development, each proposal for new work or revision of a standard, shall be accompanied by a project document, prepared by the Committee or Member proposing new work or revision of a standard, detailing:

- the purposes and the scope of the standard;
- its relevance and timeliness;
- the main aspects to be covered;
- an assessment against the *Criteria for the establishment of work priorities*;
- relevance to the Codex strategic objectives;
- information on the relation between the proposal and other existing Codex documents;
- identification of any requirement for and availability of expert scientific advice;
- identification of any need for technical input to the standard from external bodies so that this can be planned for;
- the proposed time-line for completion the new work, including the start date, the

proposed date for adoption at Step 5, and the proposed date for adoption by the Commission; the time frame for developing a standard should not normally exceed five years.

2. The decision to undertake new work or to revise standards shall be taken by the Commission taking into account a critical review conducted by the Executive Committee.

3. The critical review includes:

- examination of proposals for development/revision of standards, taking into account the "*Criteria for the Establishment of Work Priorities*", the strategic plan of the Commission and the required supporting work of independent risk assessment;
- identifying the standard setting needs of developing countries;
- advice on establishment and dissolution of committees and task forces, including *ad hoc* cross-committee task forces (in areas where work falls within several committee mandates); and
- preliminary assessment of the need for expert scientific advice and the availability of such advice from FAO, WHO or other relevant expert bodies, and the prioritisation of that advice.

4. The decision to undertake new work or revision of individual maximum residue limits for pesticides or veterinary drugs, or the maintenance of the General Standard on Food Additives², the General Standard on Contaminants and Toxins in Foods³, the Food Categorisation System and the International Numbering System, shall follow the procedures established by the Committees concerned and endorsed by the Commission.

Monitoring Progress of Standards Development

5. The Executive Committee shall review the status of development of draft standards against the time frame agreed by the Commission and shall report its findings to the Commission.

6. The Executive Committee may propose an extension of the time frame; cancellation of work; or propose that the work be undertaken by a Committee other than the one to which it was originally entrusted, including the establishment of a limited number of *ad hoc* subsidiary bodies, if appropriate.

7. The critical review process shall ensure that progress in the development of standards is consistent with the envisaged time frame, that draft standards submitted to the Commission for adoption have been fully considered at Committee level.

8. Monitoring shall take place against the time line deemed necessary and revisions in the coverage of the standard shall need to be specifically endorsed by the Commission.

This shall therefore include:

- monitoring of progress in developing standards and advising what corrective action should be taken;

² including related methods of analysis and sampling plans

³ including related methods of analysis and sampling plans

- examining proposed standards from Codex committees, before they are submitted to the Commission for adoption:
 - for consistency with the mandate of Codex, the decisions of the Commission, and existing Codex texts,
 - to ensure that the requirements of the endorsement procedure have been fulfilled, where appropriate,
 - for format and presentation, and
 - for linguistic consistency.

***PART 3. UNIFORM PROCEDURE FOR THE ELABORATION OF CODEX STANDARDS
AND RELATED TEXTS***

Steps 1, 2 and 3

- (1) The Commission decides, taking into account the outcome of the critical review conducted by the Executive Committee, to elaborate a World-wide Codex Standard and also decides which subsidiary body or other body should undertake the work. A decision to elaborate a World-wide Codex Standard may also be taken by subsidiary bodies of the Commission in accordance with the above mentioned outcome, subject to subsequent approval by the Commission at the earliest possible opportunity. In the case of Codex Regional Standards, the Commission shall base its decision on the proposal of the majority of Members belonging to a given region or group of countries submitted at a session of the Codex Alimentarius Commission.
- (2) The Secretariat arranges for the preparation of a proposed draft standard. In the case of Maximum Limits for Residues of Pesticides or Veterinary Drugs, the Secretariat distributes the recommendations for maximum limits, when available from the Joint Meetings of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues (JMPR), or the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Any other relevant information regarding risk assessment work conducted by FAO and WHO should also be made available. In the cases of milk and milk products or individual standards for cheeses, the Secretariat distributes the recommendations of the International Dairy Federation (IDF).
- (3) The proposed draft standard is sent to Members of the Commission and interested international organizations for comment on all aspects including possible implications of the proposed draft standard for their economic interests.

Step 4

The comments received are sent by the Secretariat to the subsidiary body or other body concerned which has the power to consider such comments and to amend the proposed draft standard.

Step 5

The proposed draft standard is submitted through the Secretariat to the Executive Committee for

critical review and to the Commission with a view to its adoption as a draft standard⁴. In taking any decision at this step, the Commission will give due consideration to the outcome of the critical review and to any comments that may be submitted by any of its Members regarding the implications which the proposed draft standard or any provisions thereof may have for their economic interests. In the case of Regional Standards, all Members of the Commission may present their comments, take part in the debate and propose amendments, but only the majority of the Members of the region or group of countries concerned attending the session can decide to amend or adopt the draft. In taking any decisions at this step, the Members of the region or group of countries concerned will give due consideration to any comments that may be submitted by any of the Members of the Commission regarding the implications which the proposed draft standard or any provisions thereof may have for their economic interests.

Step 6

The draft standard is sent by the Secretariat to all Members and interested international organizations for comment on all aspects, including possible implications of the draft standard for their economic interests.

Step 7

The comments received are sent by the Secretariat to the subsidiary body or other body concerned, which has the power to consider such comments and amend the draft standard.

Step 8

The draft standard is submitted through the Secretariat to the Executive Committee for critical review and to the Commission, together with any written proposals received from Members and interested international organizations for amendments at Step 8, with a view to its adoption as a Codex standard. In the case of Regional standards, all Members and interested international organizations may present their comments, take part in the debate and propose amendments but only the majority of Members of the region or group of countries concerned attending the session can decide to amend and adopt the draft.

PART 4. UNIFORM ACCELERATED PROCEDURE FOR THE ELABORATION OF CODEX STANDARDS AND RELATED TEXTS

Steps 1, 2 and 3

- (1) The Commission, on the basis of a two-thirds majority of votes cast, taking into account the outcome of the critical review conducted by the Executive Committee, shall identify those standards which shall be the subject of an accelerated elaboration process.⁵ The identification of such standards may also be made by subsidiary bodies of the Commission, on the basis of a two-thirds majority of votes cast, subject to confirmation at the earliest opportunity by the Commission.

⁴ Without prejudice to the outcome of the critical review conducted by the Executive Committee and/or any decision that may be taken by the Commission at Step 5, the proposed draft standard may be sent by the Secretariat for government comments prior to its consideration at Step 5, when, in the opinion of the subsidiary body or other body concerned, the time between the relevant session of the Commission and the subsequent session of the subsidiary body or other body concerned requires such action in order to advance the work

⁵ Relevant considerations could include, but need not be limited to, matters concerning new scientific information; new technology(ies); urgent problems related to trade or public health; or the revision or up-dating of existing standards.

- (2) The Secretariat arranges for the preparation of a proposed draft standard. In the case of Maximum Limits for Residues of Pesticides or Veterinary Drugs, the Secretariat distributes the recommendations for maximum limits, when available from the Joint Meetings of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues (JMPR), or the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Any other relevant information regarding risk assessment work conducted by FAO and WHO should also be made available. In the cases of milk and milk products or individual standards for cheeses, the Secretariat distributes the recommendations of the International Dairy Federation (IDF).
- (3) The proposed draft standard is sent to Members of the Commission and interested international organizations for comment on all aspects including possible implications of the proposed draft standard for their economic interests. When standards are subject to an accelerated procedure, this fact shall be notified to the Members of the Commission and the interested international organizations.

Step 4

The comments received are sent by the Secretariat to the subsidiary body or other body concerned which has the power to consider such comments and to amend the proposed draft standard.

Step 5

In the case of standards identified as being subject to an accelerated elaboration procedure, the draft standard is submitted through the Secretariat to the Executive Committee for critical review and to the Commission, together with any written proposals received from Members and interested international organizations for amendments, with a view to its adoption as a Codex standard. In taking any decision at this step, the Commission will give due consideration to any comments that may be submitted by any of its Members regarding the implications which the proposed draft standard or any provisions thereof may have for their economic interests.

PART 5. SUBSEQUENT PROCEDURE CONCERNING PUBLICATION OF CODEX STANDARDS

The Codex standard is published and issued to all Member States and Associate Members of FAO and/or WHO and to the international organizations concerned.

The above mentioned publications will constitute the *Codex Alimentarius*.

SUBSEQUENT PROCEDURE CONCERNING PUBLICATION AND POSSIBLE EXTENSION OF TERRITORIAL APPLICATION OF THE STANDARD

The Codex Regional Standard is published and issued to all Member States and Associate Members of FAO and/or WHO and to the international organizations concerned.

It is open to the Commission to consider at any time the possible extension of the territorial application of a Codex Regional Standard or its conversion into a World-wide Codex Standard.

**GUIDE TO THE CONSIDERATION OF STANDARDS AT STEP 8 OF THE PROCEDURE
FOR THE ELABORATION OF CODEX STANDARDS INCLUDING CONSIDERATION
OF ANY STATEMENTS RELATING TO ECONOMIC IMPACT**

1. In order:
 - (a) to ensure that the work of the Codex committee concerned is not made less valuable by the passage of an insufficiently considered amendment in the Commission;
 - (b) at the same time to provide scope for significant amendments to be raised and considered in the Commission;
 - (c) to prevent, as far as practicable, lengthy discussion in the Commission on points that have been thoroughly argued in the Codex committee concerned;
 - (d) to ensure, as far as practicable, that delegations are given sufficient warning of amendments so that they may brief themselves adequately,

amendments to Codex standards at Step 8 should, as far as practicable, be submitted in writing, although amendments proposed in the Commission would not be excluded entirely, and the following procedure should be employed:

2. When Codex standards are distributed to Member Countries prior to their consideration by the Commission at Step 8, the Secretariat will indicate the date by which proposed amendments must be received; this date will be fixed so as to allow sufficient time for such amendments to be in the hands of governments not less than one month before the session of the Commission.

3. Governments should submit amendments in writing by the date indicated and should state that they had been previously submitted to the appropriate Codex committee with details of the submission of the amendment or should give the reason why the amendment had not been proposed earlier, as the case may be.

4. When amendments are proposed during a session of the Commission, without prior notice, to a standard which is at Step 8, the Chairperson of the Commission, after consultation with the chairperson of the appropriate committee, or, if the chairperson is not present, with the delegate of the chairing country, or, in the case of subsidiary bodies which do not have a chairing country, with other appropriate persons, shall rule whether such amendments are substantive.

5. If an amendment ruled as substantive is agreed to by the Commission, it shall be referred to the appropriate Codex committee for its comments and, until such comments have been received and considered by the Commission, the standard shall not be advanced beyond Step 8 of the Procedure.

6. It will be open to any Member of the Commission to draw to the attention of the Commission any matter concerning the possible implications of a draft standard for its economic interests, including any such matter which has not, in that Member's opinion, been satisfactorily resolved at an earlier step in the Procedure for the Elaboration of Codex Standards. All the information pertaining to the matter, including the outcome of any previous consideration by the Commission or a subsidiary body thereof should be presented in writing to the Commission, together with any draft amendments to the standard which would in the opinion of the country concerned, take into account the economic implications. In considering statements concerning economic implications the Commission should have due regard to the purposes of the Codex Alimentarius concerning the protection of the health of consumers and the ensuring of fair practices in the food trade, as set forth in the General Principles of the Codex Alimentarius, as well as the economic interests of the Member concerned. It will be open

to the Commission to take any appropriate action including referring the matter to the appropriate Codex committee for its comments.

**GUIDE TO THE PROCEDURE FOR THE REVISION AND AMENDMENT
OF CODEX STANDARDS**

1. Proposals for the amendment or revision of Codex standards should be submitted to the Commission's Secretariat in good time (not less than three months) before the session of the Commission at which they are to be considered. The proposer of an amendment should indicate the reasons for the proposed amendment and should also state whether the proposed amendment had been previously submitted to and considered by the Codex committee concerned and/or the Commission. If the proposed amendment has already been considered by the Codex committee and/or Commission, the outcome of the consideration of the proposed amendment should be stated.
2. Taking into account such information regarding the proposed amendment, as may be supplied in accordance with paragraph 1 above, and the outcome of the on-going critical review conducted by the Executive Committee, the Commission will decide whether the amendment or revision of a standard is necessary. If the Commission decides in the affirmative, and the proposer of the amendment is other than a Codex committee, the proposed amendment will be referred for consideration to the appropriate Codex committee, if such committee is still in existence. If such committee is not in existence, the Commission will determine how best to deal with the proposed amendment. If the proposer of the amendment is a Codex committee, it would be open to the Commission to decide that the proposed amendment be circulated to governments for comments prior to further consideration by the sponsoring Codex Committee. In the case of an amendment proposed by a Codex Committee, it will also be open to the Commission to adopt the amendment at Step 5 or Step 8 as appropriate, where in its opinion the amendment is either of an editorial nature or of a substantive nature but consequential to provisions in similar standards adopted by it at Step 8.
3. The procedure for amending or revising a Codex standard would be as laid down in paragraphs 5 and 6 of the Introduction to the Procedure for the Elaboration of Codex Standards.
4. When the Commission has decided to amend or revise a standard, the unrevised standard will remain the applicable Codex standard until the revised standard has been adopted by the Commission.

**ARRANGEMENTS FOR THE AMENDMENT OF CODEX STANDARDS
ELABORATED BY CODEX COMMITTEES WHICH HAVE ADJOURNED SINE DIE**

1. The need to consider amending or revising adopted Codex standards arises from time to time for a variety of reasons amongst which can be:
 - (a) changes in the evaluation of food additives, pesticides and contaminants;
 - (b) finalization of methods of analysis;
 - (c) editorial amendments of guidelines or other texts adopted by the Commission and related to all or a group of Codex standards e.g. "Guidelines on Date Marking", "Guidelines on Labelling of Non-retail Containers", "Carry-over Principle";
 - (d) consequential amendments to earlier Codex standards arising from Commission decisions on currently adopted standards of the same type of products;
 - (e) consequential and other amendments arising from either revised or newly elaborated Codex standards and other texts of general applicability which have been referenced

in other Codex standards (Revision of General Principles of Food Hygiene, Codex Standard for the Labelling of Prepackaged Foods);

- (f) technological developments or economic considerations e.g. provisions concerning styles, packaging media or other factors related to composition and essential quality criteria and consequential changes in labelling provisions;

2. The "Guide to the Procedure for the Revision and Amendment of Codex Standards" covers sufficiently amendments to Codex standards which have been elaborated by still active Codex Committees. In the case of amendments proposed to Codex standards elaborated by Codex Committees which have adjourned *sine die*, the procedure places an obligation on the Commission to "determine how best to deal with the proposed amendment". In order to facilitate consideration of such amendments, the Commission has established more detailed guidance within the existing procedure for the amendment and revision of Codex standards.

3. In the case where Codex committees have adjourned *sine die*:

- (a) the Secretariat keeps under review all Codex standards originating from Codex Committees adjourned *sine die* and to determine the need for any amendments arising from decisions of the Commission, in particular amendments of the type mentioned in para. 1(a), (b), (c), (d) and those of (e) if of an editorial nature. If a need to amend the standard appears appropriate then the Secretariat should prepare a text for adoption in the Commission;
- (b) amendments of the type in para (f) and those of (e) of a substantive nature, the Secretariat in cooperation with the national secretariat of the adjourned Committee and, if possible, the Chairperson of that Committee, should agree on the need for such an amendment and prepare a working paper containing the wording of a proposed amendment and the reasons for proposing such amendment, and request comments from Member Governments: (a) on the need to proceed with such an amendment and (b) on the proposed amendment itself. If the majority of the replies received from Member Governments is affirmative on both the need to amend the standard and the suitability of the proposed wording for the amendment or an alternative proposed wording, the proposal should be submitted to the Commission with a request to approve the amendment of the standard concerned. In cases where replies do not appear to offer an uncontroversial solution then the Commission should be informed accordingly and it would be for the Commission to determine how best to proceed.

ANNEX 2

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS (CX-730)

Host Government: United States of America

Sessions:

- 1st Washington, D.C. 27-31 October, 1986
- 2nd Washington, D.C. 30 November - 4 December 1987
- 3rd Washington, D.C. 31 October - 4 November 1988
- 4th Washington, D.C. 24-27 October 1989
- 5th Washington, D.C. 16-19 October 1990
- 6th Washington, D.C. 22-25 October 1991
- 7th Washington, D.C., 20-23 October 1992
- 8th Washington, D.C., 7-10 June 1994
- 9th Washington, D.C., 5-8 December 1995
- 10th San José (Costa Rica), 29 October - 1 November 1996
- 11th Washington D.C., 15-18 September 1998
- 12th Washington, D.C., 28-31 March 2000
- 13th Charleston, South Carolina, 4 - 7 December 2001
- 14th Arlington, Virginia, 4-7 March 2003
- 15th Alexandria, Virginia, 26-29 October 2004

Terms of reference:

- (a) to determine priorities for the consideration of residues of veterinary drugs in foods;
- (b) to recommend maximum levels of such substances;
- (c) to develop codes of practice as may be required;
- (d) to consider methods of sampling and analysis for the determination of veterinary drug residues in foods.

(Extract from the Procedural Manual, 15th Edition)

ANNEX 3

MEASURES TO FACILITATE CONSENSUS⁶

The Codex Alimentarius Commission desiring that every effort should be made to reach agreement on the adoption or amendment of standards by consensus, recommends the following measures to facilitate consensus:

- Refraining from submitting proposals in the step process where the scientific basis is not well established on current data and, where necessary, carry out further studies in order to clarify controversial issues;
- Providing for thorough discussions and documentation of the issues at meetings of the committees concerned;
- Organizing informal meetings of the parties concerned where disagreements arise, provided that the objectives of any such meetings are clearly defined by the Committee concerned and that participation is open to all interest delegations and observers in order to preserve transparency;
- Redefining, where possible, the scope of the subject matter being considered for the elaboration of standards in order to cut out issues on which consensus could not be reached;
- Providing that matters are not progressed from step to step until all relevant concerns are taken into account and adequate compromises worked out;
- Emphasizing to Committees and their Chairpersons that matters should not be passed on to the Commission until such time as consensus has been achieved at the technical level;
- Facilitating the increased involvement and participation of developing countries.

⁶ Decision of the 26th Session of the Commission, 2003.

ANNEX 4

GENERAL PRINCIPLES OF THE CODEX ALIMENTARIUS⁷

PURPOSE OF THE CODEX ALIMENTARIUS

1. The Codex Alimentarius is a collection of internationally adopted food standards presented in a uniform manner. These food standards aim at protecting consumers' health and ensuring fair practices in the food trade. The Codex Alimentarius also includes provisions of an advisory nature in the form of codes of practice, guidelines and other recommended measures intended to assist in achieving the purposes of the Codex Alimentarius. The publication of the Codex Alimentarius is intended to guide and promote the elaboration and establishment of definitions and requirements for foods to assist in their harmonization and in doing so to facilitate international trade.

SCOPE OF THE CODEX ALIMENTARIUS

2. The Codex Alimentarius includes standards for all the principle foods, whether processed, semi-processed or raw, for distribution to the consumer. Materials for further processing into foods should be included to the extent necessary to achieve the purposes of the Codex Alimentarius as defined. The Codex Alimentarius includes provisions in respect of food hygiene, food additives, pesticide residues, contaminants, labelling and presentation, methods of analysis and sampling. It also includes provisions of an advisory nature in the form of codes of practice, guidelines and other recommended measures.

NATURE OF CODEX STANDARDS

3. Codex standards contain requirements for food aimed at ensuring for the consumer a sound, wholesome food product free from adulteration, correctly labelled and presented. A Codex standard for any food or foods should be drawn up in accordance with the Format for Codex Commodity Standards and contain, as appropriate, the criteria listed therein.

ACCEPTANCE OF CODEX COMMODITY STANDARDS

4.A. A Codex standard may be accepted by a country in accordance with its established legal and administrative procedures in respect of distribution of the product concerned, whether imported or home produced, within its territorial jurisdiction in the following ways:

(i) Full acceptance

- (a) Full acceptance means that the country concerned will ensure that a product to which the standard applies will be permitted to be distributed freely, in accordance with (c) below, within its territorial jurisdiction under the name and description laid down in the standard, provided that it complies with all the relevant requirements of the standard.
- (b) The country will also ensure that products not complying with the standard will not be permitted to be distributed under the name and description laid down in the standard.
- (c) The distribution of any sound products conforming with the standard will not be hindered by any legal or administrative provisions in the country concerned relating to the health of the

⁷ Procedural Manual of the Codex Alimentarius Commission (14th Edition).

consumer or to other food standard matters except for considerations of human, plant or animal health which are not specifically dealt with in the standard.

(ii) Acceptance with specified deviations

Acceptance with specified deviations means that the country concerned gives acceptance, as defined in paragraph 4.A(i), to the standard with the exception of such deviations as are specified in detail in its declaration of acceptance; it being understood that a product complying with the standard as qualified by these deviations will be permitted to be distributed freely within the territorial jurisdiction of the country concerned. The country concerned will further include in its declaration of acceptance a statement of the reasons for these deviations, and also indicate:

- (a) whether products fully conforming to the standard may be distributed freely within its territorial jurisdiction in accordance with paragraph 4.A(i);
- (b) whether it expects to be able to give full acceptance to the standard and, if so, when.

(iii) Free distribution

A declaration of free distribution means that the country concerned undertakes that products conforming with a Codex commodity standard may be distributed freely within its territorial jurisdiction insofar as matters covered by the Codex commodity standard are concerned.

B. A country which considers that it cannot accept the standard in any of the ways mentioned above should indicate:

- (i) whether products conforming to the standard may be distributed freely within its territorial jurisdiction;
- (ii) in what ways its present or proposed requirements differ from the standard, and, if possible the reasons for these differences.

C. (i) A country which accepts a Codex standard according to one of the provisions of 4.A is responsible for the uniform and impartial application of the provisions of the standard as accepted, in respect of all home-produced and imported products distributed within its territorial jurisdiction. In addition, the country should be prepared to offer advice and guidance to exporters and processors of products for export to promote understanding of and compliance with the requirements of importing countries which have accepted a Codex standard according to one of the provisions of 4.A.

(ii) Where, in an importing country, a product claimed to be in compliance with a Codex standard is found not to be in compliance with that standard, whether in respect of the label accompanying the product or otherwise, the importing country should inform the competent authorities in the exporting country of all the relevant facts and in particular the details of the origin of the product in question (name and address of the exporter), if it is thought that a person in the exporting country is responsible for such non-compliance.

ACCEPTANCE OF CODEX GENERAL STANDARDS

5.A. A Codex general standard may be accepted by a country in accordance with its established legal and administrative procedures in respect of the distribution of products to which the general standard applies, whether imported or home-produced, within its territorial jurisdiction in the following ways:

(i) Full acceptance

Full acceptance of a general standard means that the country concerned will ensure, within its territorial jurisdiction, that a product to which the general standard applies will comply with all the relevant requirements of the general standard except as otherwise provided in a Codex commodity standard. It also means that the distribution of any sound products conforming with the standard will not be hindered by any legal or administrative provisions in the country concerned, which relate to the health of the consumer or to other food standard matters and which are covered by the requirements of the general standard.

(ii) Acceptance with specified deviations

Acceptance with specified deviations means that the country concerned gives acceptance, as defined in paragraph 5.A(i), to the general standard with the exception of such deviations as are specified in detail in its declaration of acceptance. The country concerned will further include in its declaration of acceptance a statement of the reasons for these deviations, and also indicate whether it expects to be able to give full acceptance to the general standard and, if so, when.

(iii) Free distribution

A declaration of free distribution means that the country concerned undertakes that products conforming with the relevant requirements of a Codex general standard may be distributed freely within its territorial jurisdiction insofar as matters covered by the Codex general standard are concerned.

B. A country which considers that it cannot accept the general standard in any of the ways mentioned above should indicate in what ways its present or proposed requirements differ from the general standard, and if possible, the reasons for these differences.

C. (i) A country which accepts a general standard according to one of the provisions of paragraph 5.A is responsible for the uniform and impartial application of the provisions of the standard as accepted, in respect of all home produced and imported products distributed within its territorial jurisdiction. In addition, the country should be prepared to offer advice and guidance to exporters and processors of products for export to promote understanding of and compliance with the requirements of importing countries which have accepted a general standard according to one of the provisions of paragraph 5.A.

(ii) Where, in an importing country, a product claimed to be in compliance with a general standard is found not to be in compliance with that standard, whether in respect of the label accompanying the product or otherwise, the importing country should inform the competent authorities in the exporting country of all the relevant facts and in particular the details of the origin of the product in question (name and address of the exporter), if it is thought that a person in the exporting country is responsible for such non-compliance.

***ACCEPTANCE OF CODEX MAXIMUM LIMITS FOR RESIDUES OF PESTICIDES
AND VETERINARY DRUGS IN FOOD***

6.A. A Codex maximum limit for residues of pesticides or veterinary drugs in food may be accepted by a country in accordance with its established legal and administrative procedures in respect of the distribution within its territorial jurisdiction of (a) home-produced and imported food or (b) imported food only, to which the Codex maximum limit applies in the ways set forth below. In addition, where a Codex maximum limit applies to a group of foods not individually named, a country

accepting such Codex maximum limit in respect of other than the group of foods, shall specify the foods in respect of which the Codex maximum limit is accepted.

(i) Full acceptance

Full acceptance of a Codex maximum limit for residues of pesticides or veterinary drugs in food means that the country concerned will ensure, within its territorial jurisdiction, that a food, whether home-produced or imported, to which the Codex maximum limit applies, will comply with that limit. It also means that the distribution of a food conforming with the Codex maximum limit will not be hindered by any legal or administrative provisions in the country concerned which relate to matters covered by the Codex maximum limit.

(ii) Free distribution

A declaration of free distribution means that the country concerned undertakes that products conforming with the Codex maximum limit for residues of pesticides or veterinary drugs in food may be distributed freely within its territorial jurisdiction insofar as matters covered by the Codex maximum limit are concerned.

B. A country which considers that it cannot accept the Codex maximum limit for residues of pesticides or veterinary drugs in foods in any of the ways mentioned above should indicate in what ways its present or proposed requirements differ from the Codex maximum limit and, if possible, the reasons for these differences.

C. A country which accepts a Codex maximum limit for residues of pesticides or veterinary drugs in food according to one of the provisions of paragraph 6.A should be prepared to offer advice and guidance to exporters and processors of food for export to promote understanding of and compliance with the requirements of importing countries which have accepted a Codex maximum limit according to one of the provisions of paragraph 6.A.

D. Where, in an importing country, a food claimed to be in compliance with a Codex maximum limit is found not to be in compliance with the Codex maximum limit, the importing country should inform the competent authorities in the exporting country of all the relevant facts and, in particular, the details of the origin of the food in question (name and address of the exporter), if it is thought that a person in the exporting country is responsible for such non-compliance.

WITHDRAWAL OR AMENDMENT OF ACCEPTANCE

7. The withdrawal or amendment of acceptance of a Codex standard or a Codex maximum limit for residues of pesticides or veterinary drugs in food by a country shall be notified in writing to the Codex Alimentarius Commission's Secretariat who will inform all Member States and Associate Members of FAO and WHO of the notification and its date of receipt. The country concerned should provide the information required under paragraphs 4.A(iii), 5.A(iii), 4.B, 5.B or 6.B above, whichever is appropriate. It should also give as long a notice of the withdrawal or amendment as is practicable.

REVISION OF CODEX STANDARDS

8. The Codex Alimentarius Commission and its subsidiary bodies are committed to revision as necessary of Codex standards and related texts to ensure that they are consistent with and reflect current scientific knowledge and other relevant information. When required, a standard or related text shall be revised or removed using the same procedures as followed for the elaboration of a new standard. Each member of the Codex Alimentarius Commission is responsible for identifying, and

presenting to the appropriate committee, any new scientific and other relevant information which may warrant revision of any existing Codex standards or related texts.

GUIDELINES FOR THE ACCEPTANCE PROCEDURE FOR CODEX STANDARDS

THE IMPORTANCE OF A RESPONSE TO EVERY NOTIFICATION

1. The Codex Alimentarius is the record of Codex Standards and of acceptances or other notifications by Member Countries or international organizations to which competence in the matter has been transferred by their Member States. It is revised regularly to take account of the issue of new or amended standards and the receipt of notifications. It is important that governments respond to every issue of new or amended standards. Governments should aim at giving formal acceptance to the standards. If acceptance or free circulation cannot be given unconditionally, the deviations or conditions, and the reasons, can be included in the response. Early and regular responses will ensure that the Codex Alimentarius can be kept up to date so as to serve as an indispensable reference for governments and international traders.
2. Governments should ensure that the information in the Codex Alimentarius reflects the up to date position. When changing national laws or practices the need for a notification to the Codex Secretariat should always be kept in mind.
3. The Codex procedure for elaboration of standards enables governments to participate at all stages. Governments should be able to make an early response to the issue of a Codex standard and should do their utmost to be ready to do so.

THE CODEX ALIMENTARIUS: NOT A SUBSTITUTE FOR, OR ALTERNATIVE TO, REFERRING TO NATIONAL LEGISLATION

4. Every country's laws and administrative procedures contain provisions which it is essential to understand and comply with. It is usually the practice to take steps to obtain copies of relevant legislation and/or to obtain professional advice about compliance. The Codex Alimentarius is a comparative record of the substantive similarities and differences between Codex Standards and corresponding national legislation. The Codex Standard will not normally deal with general matters of human, plant or animal health or with trade marks. The language which is required on labels will be a matter for national legislation and so will import licences and other administrative procedures.
5. The responses by governments should show clearly which provisions of the Codex Standard are identical to, similar to or different from, the related national requirements. General statements that national laws must be complied with should be avoided or accompanied by details of national provisions which require attention. Judgement will sometimes be required where the national law is in a different form or where it has different provisions.

OBLIGATIONS UNDER THE ACCEPTANCE PROCEDURE

6. The obligations which a country undertakes under the acceptance procedure are included in paragraph 4 of the General Principles. Paragraph 4.A(i)(a) provides for free distribution of conforming products, 4.A(i)(b) with the need to ensure that products which do not conform may not be distributed "under the name and description laid down". Paragraph 4.A(i)(c) is a general requirement not to hinder the distribution of sound products, except for matters relating to human, plant or animal health, not specifically dealt with in the standard. Similar provisions are included in Acceptance with Specified Deviations.

7. The essential difference between acceptances and notifications of free distribution is that a country which accepts, undertakes to enforce the Codex standard and to accept all the obligations set out in the General Principles subject to any specified deviations.

8. The Codex Committee on General Principles (CCGP) and the Commission (CAC) have reviewed the acceptance procedure and notifications by governments on a number of occasions. While recognizing that difficulties can arise from time to time in reconciling the obligations of the acceptance procedure with the laws and administrative procedures of a Member Country, the CCGP and the CAC have determined that the obligations are essential to the work and status of the CAC and that they should not be weakened in any way. The purpose of these guidelines therefore is to assist governments when they are considering how, in the light of the objectives of the acceptance procedure, to respond to Codex Standards.

THE RETURN OF THE RESPONSE

9. The principal decision which is required is whether to notify an acceptance according to one of the methods prescribed, or non acceptance as provided for in 4.B. Free distribution (4.A(iii)) does not carry with it the obligation to prevent non conforming products from being circulated, and it may be useful in cases where there is no corresponding national standard and no intention to introduce one.

THE NEED FOR AN INFORMED, RESPONSIBLE JUDGEMENT WHEN COMPARING THE CODEX STANDARD WITH NATIONAL LAWS

10. There will be some occasions when the detail in the Codex Standard is identical with national laws. Difficulties will arise however when national laws are in a different form, contain different figures or no figures at all, or in cases where there may be no standard in the country which corresponds in substance to the Codex Standard. The authority responsible for notifying the response to the CAC is urged to do its best to overcome any such difficulties by the exercise of its best endeavours and to respond, after such consultations as may be appropriate with the national organizations. The grounds on which the judgement has been based can be made clear in the notification. It may well be that they will not be such as to justify an acceptance, because of the obligations to stop the distribution of non conforming products, but a statement of free circulation should be possible on the basis of the facts and practices of each case. If there was a court decision or change in the law or practice subsequently, an amending response should be made.

PRESUMPTIVE STANDARDS

11. A presumptive standard is one which is assumed to be the standard in the absence of any other. (A presumption in law is the assumption of the truth of anything until the contrary is proved.) Some countries have said that a Codex MRL is the presumptive limit for a pesticide residue. Countries may be able and willing to regard a Codex Standard as the presumptive standard in cases where there is no corresponding standard, code of practice or other accepted expression of the "nature, substance or quality" of the food. A country need not apply the presumption to all the provisions of the standard if the details of its additives, contaminants, hygiene or labelling rules are different from those in the standard. In such a case the provisions in the Codex Standard defining the description, essential composition and quality factors relating to the specified name and description could still be the presumptive standard for those matters.

12. The justification for regarding the Codex Standard as a presumptive standard is the fact that it is the minimum standard for a food elaborated in the CAC "so as to ensure a sound, wholesome product free from adulteration, correctly labelled and presented". (General Principles, Paragraph 3.) The word minimum does not have any pejorative connotations: it simply means the level of quality

and soundness of a product judged by consensus to be appropriate for trade internationally and nationally.

13. Whether a presumptive standard would merit an acceptance would depend on whether the country concerned could say that non conforming products could not be distributed under the same name and description laid down in the standard. However it would enable a declaration of free circulation to be made and countries are asked to give the idea serious consideration.

FORMAT AND CONTENT OF CODEX STANDARDS

Scope

14. This section, together with the name of the standard and the name and description laid down in the labelling section, should be examined in order to assess whether the obligations of the acceptance procedure can properly be accepted.

Description, essential composition and quality factors

15. These sections will define the minimum standard for the food. They will be the most difficult to address unless by chance the details are virtually identical (i.e. ignoring significant matters of editorial expression or format). However, a country which has taken part in the elaboration of the standard either by attending the meetings or by sending comments under the Step Procedure has, no doubt, consulted national organizations on the extent to which the draft provisions in the standard would be acceptable nationally. This factual information needs to be turned into a formal response when the standard is sent out for acceptance. Countries are asked to do their best to exercise an informal judgement on lines discussed in Paragraph 7 above. Some of the quality criteria e.g. allowances for defects may represent good manufacturing practice or be left to trade contracts. This will have to be taken into account. A free distribution response ought to be possible in most cases.

Food Additives

16. The food additives included in the standard have been assessed and cleared by JECFA. The Commodity Committee and the CCFAC have assessed technological need and safety in use. If national laws are different, all the detailed differences should be reported. It should be borne in mind, however, that the aim of international food standardization work is to harmonize policies and attitudes as much as possible. Therefore every effort should be made to keep deviations to the minimum.

Contaminants

17. If national limits apply they should be quoted if not the same as those laid down in the Codex Standard. Where general laws about safety, health or nature of the food apply, the limits quoted in the standard could properly be regarded as representing those which are unavoidable in practice and within safety limits.

Hygiene and Weights and Measures

18. If national requirements are different they should be reported.

Labelling

19. The General Standard for the Labelling of Prepackaged Foods represents the international consensus on information to be included on the labels of all foods.

20. Governments are exhorted to use the General Standard as a basis for their national legislation and to keep differences to an absolute minimum especially those of detail or minutiae. Governments should observe the footnote to the Scope section and should ensure that all compulsory provisions relating to presentation of information which are additional to, and different from, those in the standard should be notified. Any other compulsory provisions in national legislation should also be notified if they are not provided for in the Codex standard. The labelling provisions in Codex standards include sections of the revised General Standard by reference. When accepting a Codex commodity standard, a country which has already accepted and responded to the General Standard can then refer to the terms of that acceptance in any subsequent responses. As much specific information as is relevant and helpful should be given. In particular, this should include the name and description relating to the food, the interpretation of any special requirements relating to the law or custom of the country, any additional details about presentation of the mandatory information and detailed differences if any in the labelling requirements e.g. in relation to class names, declaration of added water, declaration of origin. It will be assumed that the language(s) in which the particulars should be given will be as indicated by national legislation or custom.

Methods of Analysis and Sampling

21. The obligations which a country assumes in accepting the following Codex Defining Methods of Analysis included in Codex standards are as follows⁸:

- (a) Codex Defining Methods of Analysis (Type I) are subject to acceptance by governments just as are the provisions which they define and which form part of Codex standards.

"Full acceptance" of a Codex Defining Method means the acceptance that the value provided for in a Codex standard is defined by means of the Codex method. In determining compliance with the value in the Codex standard, governments undertake to use the Codex Defining Method, especially in cases of disputes involving the results of analysis.

"Non acceptance" of Codex Defining Method or acceptance of Codex standards with substantive deviations in the Codex Defining Methods means acceptance of the Codex standard with specified deviation.

- (b) The "acceptance" of Codex standards containing Codex Reference Methods of Analysis (Type II) means the recognition that Codex Reference Methods are methods the reliability of which has been demonstrated on the basis of internationally acceptable criteria. They are, therefore, obligatory for use, i.e. subject to acceptance by governments, in disputes involving the results of analysis. "Non acceptance" of the Codex Reference Method or acceptance of Codex standards with substantive deviations in the Codex Reference Methods for use in disputes involving methods of analysis, should be taken to mean acceptance of the Codex standard with specified deviation.
- (c) The "acceptance" of Codex standards containing Codex Alternative Approved Methods of Analysis (Type III) means the recognition that Codex Alternative Approved Methods are methods the reliability of which has been demonstrated in

⁸ The Committee on General Principles, when elaborating these Guidelines, noted that the Classification of Methods was under review by the Codex Committee on Methods of Analysis and Sampling and that the application of Part (b) particularly could be unnecessarily restrictive.

terms of internationally acceptable criteria. They are recommended for use in food control, inspection or for regulatory purposes.

"Non acceptance" of a Codex Alternative Approved Method does not constitute a deviation from the Codex standard.

- (d) Since the reliability of the Tentative Methods (Type IV) has not yet been endorsed by the Codex Committee on Methods of Analysis and Sampling on the basis of the internationally accepted criteria, it follows that they cannot be regarded as final Codex methods. Type IV methods may, eventually become Type I, II or III methods with the resultant implications regarding the acceptance of Codex methods. Type IV methods are, therefore, not recommended as Codex methods until their reliability has been recognized by the CCMAS. They may be included in draft Codex standards or in Codex standards provided their non approved status is clearly indicated.

SUMMARY

22. Governments are urged to respond to every issue of Codex standards. The inclusion of responses in the Codex Alimentarius will enable the CAC and Member Governments to address the question of closer approximation of international and national requirements. Governments are urged to take the Codex standard fully into consideration when changing their national laws. The Codex Alimentarius will always be an invaluable reference for governments and for international traders although national legislation must always be consulted and complied with.

ANNEX 5

SPS Committee's clarification "how the Committee would differentiate standards, guidelines or recommendations in relation to the implementation of the SPS Agreement"

Geneva, 19 March 1998

Dear Mr. Orriss,

Your letter of 29 September 1997 was discussed by the Committee on Sanitary and Phytosanitary Measures ("the Committee") at its meetings of October 1997 and March 1998. The Committee instructed me to forward to you the following response.

By way of background, it must be clearly understood that the Committee cannot formally interpret the provisions of the SPS Agreement. This can be done only by the WTO Ministerial Conference or General Council, or indirectly through the dispute settlement process with regard to particular cases. Nonetheless, the Committee is required to carry out the functions necessary to implement the Agreement and the furtherance of its objectives and thus may express views, where appropriate, on the meaning of particular terms and provisions of the Agreement.

With respect to your first question on "how the Committee would differentiate standards, guidelines or recommendations in relation to the implementation of the SPS Agreement", Annex A of the SPS Agreement defines *international standards, guidelines and recommendations* as follows:

"(a) for food safety, the standards, guidelines and recommendations established by the Codex Alimentarius Commission relating to food additives, veterinary drug and pesticide residues, contaminants, methods of analysis and sampling, and codes and guidelines of hygienic practice; ..."

This definition makes no distinction between standards, guidelines and recommendations. The SPS Agreement does not provide specific definitions for the terms "standards", "guidelines" or "recommendations".

Throughout the text of the SPS Agreement, the terms "international standards, guidelines or recommendations" always appear together. Article 3.1 of the SPS Agreement states that "[t]o harmonize sanitary and phytosanitary measures on as wide a basis as possible, Members shall base their sanitary or phytosanitary measures on international standards, guidelines or recommendations ...". Article 3.2 indicates that sanitary measures which "... conform to international standards, guidelines or recommendations shall be deemed to be necessary to protect human, animal or plant life or health, and presumed to be consistent with the relevant provisions of this Agreement ...". Article 3.3 provides that "Members may introduce or maintain sanitary or phytosanitary measures which result in a higher level of sanitary or phytosanitary protection than would be achieved by measures based on the relevant international standards, guidelines or recommendations, if there is a scientific justification ...". In no case do these provisions differentiate between the three terms "standards", "guidelines" or "recommendations".

The Committee noted that there is no legal obligation on Members to apply Codex standards, guidelines and recommendations and, in accordance with the terms of Article 3 of the SPS Agreement, Members may choose to apply them or not. The Committee observed that how a Codex text was applied depended on its substantive content rather than the category of that text (e.g., commodity standards, MRLs, codes of practice, guidelines). This might have some bearing on how a Member could show that its measure is based on an international standard, guideline or recommendation in the context of Article 3 of the SPS Agreement. For example, a Codex standard, such as an MRL which represented a specific numeric value, may provide a higher degree of precision

than much of the content of a guideline or other Codex text. On the other hand, the Committee considered that guidelines and recommendations are intended to allow greater discretion as to the choice of measures which can be regarded as being based on the guideline or recommendation. However, the Committee was of the view that Codex work should not be constrained by this question. The Committee considers it to be an internal decision of the Codex Alimentarius Commission regarding the type and content of the texts it develops to address issues before it.

With respect to your second question on "the status the Committee would assign to Codex regional standards and related texts", in its discussions Members noted that regional standards are not included in the definition of international standards provided by Annex A of the SPS Agreement, cited above. The Committee recognized that, even if they were based on scientific evidence, regional standards were meant to apply only within a particular geographic region. However, Members do recognize that such scientifically-sound regional standards could become the foundation for the creation and adoption of international standards.

Yours sincerely,

Alex Thiermann
Chairman
Committee on Sanitary and Phytosanitary Measures

ANNEX 6

WORKING PRINCIPLES FOR RISK ANALYSIS FOR APPLICATION IN THE FRAMEWORK OF THE CODEX ALIMENTARIUS

SCOPE

- 1) These principles for risk analysis are intended for application in the framework of the Codex Alimentarius.
- 2) The objective of these Working Principles is to provide guidance to the Codex Alimentarius Commission and the joint FAO/WHO expert bodies and consultations, so that food safety and health aspects of Codex standards and related texts are based on risk analysis.
- 3) Within the framework of the Codex Alimentarius Commission and its procedures, the responsibility for providing advice on risk management lies with the Commission and its subsidiary bodies (risk managers), while the responsibility for risk assessment lies primarily with the joint FAO/WHO expert bodies and consultations (risk assessors).

RISK ANALYSIS - GENERAL ASPECTS

- 4) The risk analysis used in Codex should be:
 - applied consistently;
 - open, transparent and documented;
 - conducted in accordance with both the *Statements of Principle Concerning the Role of Science in the Codex Decision-Making Process and the Extent to Which Other Factors are Taken into Account and the Statements of Principle Relating to the Role of Food Safety Risk Assessment*; and
 - evaluated and reviewed as appropriate in the light of newly generated scientific data.
- 5) The risk analysis should follow a structured approach comprising the three distinct but closely linked components of risk analysis (risk assessment, risk management and risk communication) as defined by the Codex Alimentarius Commission⁹, each component being integral to the overall risk analysis.
- 6) The three components of risk analysis should be documented fully and systematically in a transparent manner. While respecting legitimate concerns to preserve confidentiality, documentation should be accessible to all interested parties¹⁰.
- 7) Effective communication and consultation with all interested parties should be ensured throughout the risk analysis.

⁹ See *Definitions of Risk Analysis Terms Related to Food Safety*, Codex Alimentarius Commission Procedural Manual.

¹⁰ For the purpose of the present document, the term "interested parties" refers to "risk assessors, risk managers, consumers, industry, the academic community and, as appropriate, other relevant parties and their representative organizations" (see definition of "Risk Communication")

8) The three components of risk analysis should be applied within an overarching framework for management of food related risks to human health.

9) There should be a functional separation of risk assessment and risk management, in order to ensure the scientific integrity of the risk assessment, to avoid confusion over the functions to be performed by risk assessors and risk managers and to reduce any conflict of interest. However, it is recognized that risk analysis is an iterative process, and interaction between risk managers and risk assessors is essential for practical application.

10) When there is evidence that a risk to human health exists but scientific data are insufficient or incomplete, the Codex Alimentarius Commission should not proceed to elaborate a standard but should consider elaborating a related text, such as a code of practice, provided that such a text would be supported by the available scientific evidence.¹¹

11) Precaution is an inherent element of risk analysis. Many sources of uncertainty exist in the process of risk assessment and risk management of food related hazards to human health. The degree of uncertainty and variability in the available scientific information should be explicitly considered in the risk analysis. Where there is sufficient scientific evidence to allow Codex to proceed to elaborate a standard or related text, the assumptions used for the risk assessment and the risk management options selected should reflect the degree of uncertainty and the characteristics of the hazard.

12) The needs and situations of developing countries should be specifically identified and taken into account by the responsible bodies in the different stages of the risk analysis.

RISK ASSESSMENT POLICY

13) Determination of risk assessment policy should be included as a specific component of risk management.

14) Risk assessment policy should be established by risk managers in advance of risk assessment, in consultation with risk assessors and all other interested parties. This procedure aims at ensuring that the risk assessment is systematic, complete, unbiased and transparent.

15) The mandate given by risk managers to risk assessors should be as clear as possible.

16) Where necessary, risk managers should ask risk assessors to evaluate the potential changes in risk resulting from different risk management options.

RISK ASSESSMENT¹²

17) The scope and purpose of the particular risk assessment being carried out should be clearly stated and in accordance with risk assessment policy. The output form and possible alternative outputs of the risk assessment should be defined

18) Experts responsible for risk assessment should be selected in a transparent manner on the basis of their expertise, experience, and their independence with regard to the interests involved. The procedures used to select these experts should be documented including a public declaration of any potential conflict of interest. This declaration should also identify and detail their individual expertise, experience and independence. Expert bodies and consultations should ensure effective participation of experts from different parts of the world, including experts from developing countries.

¹¹ Statement adopted by the 24th Session of the Commission (ALINORM 01/41, paras. 81-83)

¹² Reference is made to the *Statements of Principle Relating to the Role of Food Safety Risk Assessment*

- 19) Risk assessment should be conducted in accordance with the *Statements of Principle Relating to the Role of Food Safety Risk Assessment* and should incorporate the four steps of the risk assessment, i.e. hazard identification, hazard characterization, exposure assessment and risk characterization.
- 20) Risk assessment should be based on all available scientific data. It should use available quantitative information to the greatest extent possible. Risk assessment may also take into account qualitative information.
- 21) Risk assessment should take into account relevant production, storage and handling practices used throughout the food chain including traditional practices, methods of analysis, sampling and inspection and the prevalence of specific adverse health effects.
- 22) Risk assessment should seek and incorporate relevant data from different parts of the world, including that from developing countries. These data should particularly include epidemiological surveillance data, analytical and exposure data. Where relevant data are not available from developing countries, the Commission should request that FAO/WHO initiate time-bound studies for this purpose. The conduct of the risk assessment should not be inappropriately delayed pending receipt of these data; however, the risk assessment should be reconsidered when such data are available.
- 23) Constraints, uncertainties and assumptions having an impact on the risk assessment should be explicitly considered at each step in the risk assessment and documented in a transparent manner. Expression of uncertainty or variability in risk estimates may be qualitative or quantitative, but should be quantified to the extent that is scientifically achievable.
- 24) Risk assessments should be based on realistic exposure scenarios, with consideration of different situations being defined by risk assessment policy. They should include consideration of susceptible and high-risk population groups. Acute, chronic (including long-term), cumulative and/or combined adverse health effects should be taken into account in carrying out risk assessment, where relevant.
- 25) The report of the risk assessment should indicate any constraints, uncertainties, assumptions and their impact on the risk assessment. Minority opinions should also be recorded. The responsibility for resolving the impact of uncertainty on the risk management decision lies with the risk manager, not the risk assessors.
- 26) The conclusion of the risk assessment including a risk estimate, if available, should be presented in a readily understandable and useful form to risk managers and made available to other risk assessors and interested parties so that they can review the assessment.

RISK MANAGEMENT

- 27) While recognizing the dual purposes of the Codex Alimentarius are protecting the health of consumers and ensuring fair practices in the food trade, Codex decisions and recommendations on risk management should have as their primary objective the protection of the health of consumers. Unjustified differences in the level of consumer health protection to address similar risks in different situations should be avoided.

28) Risk management should follow a structured approach including preliminary risk management activities¹³, evaluation of risk management options, monitoring and review of the decision taken. The decisions should be based on risk assessment, and taking into account, where appropriate, other legitimate factors relevant for the health protection of consumers and for the promotion of fair practices in food trade, in accordance with the *Criteria for the Consideration of the Other Factors Referred to in the Second Statement of Principles*¹⁴.

29) The Codex Alimentarius Commission and its subsidiary bodies, acting as risk managers in the context of these Working Principles, should ensure that the conclusion of the risk assessment is presented before making final proposals or decisions on the available risk management options, in particular in the setting of standards or maximum levels, bearing in mind the guidance given in paragraph 10.

30) In achieving agreed outcomes, risk management should take into account relevant production, storage and handling practices used throughout the food chain including traditional practices, methods of analysis, sampling and inspection, feasibility of enforcement and compliance, and the prevalence of specific adverse health effects.

31) The risk management process should be transparent, consistent and fully documented. Codex decisions and recommendations on risk management should be documented, and where appropriate clearly identified in individual Codex standards and related texts so as to facilitate a wider understanding of the risk management process by all interested parties.

32) The outcome of the preliminary risk management activities and the risk assessment should be combined with the evaluation of available risk management options in order to reach a decision on management of the risk.

33) Risk management options should be assessed in terms of the scope and purpose of risk analysis and the level of consumer health protection they achieve. The option of not taking any action should also be considered.

34) In order to avoid unjustified trade barriers, risk management should ensure transparency and consistency in the decision-making process in all cases. Examination of the full range of risk management options should, as far as possible, take into account an assessment of their potential advantages and disadvantages. When making a choice among different risk management options, which are equally effective in protecting the health of the consumer, the Commission and its subsidiary bodies should seek and take into consideration the potential impact of such measures on trade among its Member countries and select measures that are no more trade-restrictive than necessary.

35) Risk management should take into account the economic consequences and the feasibility of risk management options. Risk management should also recognize the need for alternative options in the establishment of standards, guidelines and other recommendations, consistent with the protection of consumers' health. In taking these elements into consideration, the Commission and its subsidiary bodies should give particular attention to the circumstances of developing countries.

¹³ For the purpose of these Principles, preliminary risk management activities are taken to include: identification of a food safety problem; establishment of a risk profile; ranking of the hazard for risk assessment and risk management priority; establishment of risk assessment policy for the conduct of the risk assessment; commissioning of the risk assessment; and consideration of the result of the risk assessment.

¹⁴ These criteria have been adopted by the 24th Session of the Commission (see Procedural Manual 12th Edition - Appendix, page 165)

36) Risk management should be a continuing process that takes into account all newly generated data in the evaluation and review of risk management decisions. Food standards and related texts should be reviewed regularly and updated as necessary to reflect new scientific knowledge and other information relevant to risk analysis.

RISK COMMUNICATION

37) Risk communication should:

- (i) promote awareness and understanding of the specific issues under consideration during the risk analysis;
- (ii) promote consistency and transparency in formulating risk management options/recommendations;
- (iii) provide a sound basis for understanding the risk management decisions proposed;
- (iv) improve the overall effectiveness and efficiency of the risk analysis;
- (v) strengthen the working relationships among participants;
- (vi) foster public understanding of the process, so as to enhance trust and confidence in the safety of the food supply;
- (vii) promote the appropriate involvement of all interested parties; and
- (viii) exchange information in relation to the concerns of interested parties about the risks associated with food.

38) Risk analysis should include clear, interactive and documented communication, amongst risk assessors (Joint FAO/WHO expert bodies and consultations) and risk managers (Codex Alimentarius Commission and its subsidiary bodies), and reciprocal communication with member countries and all interested parties in all aspects of the process.

39) Risk communication should be more than the dissemination of information. Its major function should be to ensure that all information and opinion required for effective risk management is incorporated into the decision making process.

40) Risk communication involving interested parties should include a transparent explanation of the risk assessment policy and of the assessment of risk, including the uncertainty. The need for specific standards or related texts and the procedures followed to determine them, including how the uncertainty was dealt with, should also be clearly explained. It should indicate any constraints, uncertainties, assumptions and their impact on the risk analysis, and minority opinions that had been expressed in the course of the risk assessment (see para.25).

41) The guidance on risk communication in this document is addressed to all those involved in carrying out risk analysis within the framework of Codex Alimentarius. However, it is also of importance for this work to be made as transparent and accessible as possible to those not directly engaged in the process and other interested parties while respecting legitimate concerns to preserve confidentiality (See para. 6).

ANNEX 7

Consideration of Risk Analysis in CCRVDF (relevant extracts from the report of the CCRVDF)

8th Session of CCRVDF (June 1994) (ALINORM 95/31, paras 39-41)

At the request of the 20th Session of the Commission (1993) a paper entitled *Risk Assessment Procedures Used by the Codex Alimentarius Commission and its Subsidiary an Advisory Bodies* (ALINORM 93/37), prepared by a consultant Dr. S. Hathaway (New Zealand) was reviewed and discussed by the Committee.

39. The Committee supported the principles of the Hathaway paper and the view that the establishment of MRLs for residues of veterinary drugs should continued to be linked to the risk-based ADI (Acceptable Daily Intake). In this regard the Committee noted that its procedures and those of JECFA were in general consistent with the principles enunciated in the paper.

40. The Committee also agreed in principles that the use of risk analysis procedures should be extended further in the Codex Procedures for the elaboration of standards. Some delegations were of the opinion that the roles of the expert committees and the Codex committees in regard to risk assessment and risk management respectively should be clarified. However, it was noted that the overall Codex procedures had to take into account those Committees such as Food Hygiene and Meat Hygiene which did not receive independent external advise on a regular basis.

41. The Committee expressed concern at the fact that the use of the various expression used by Codex in relation to risk analysis had not been harmonised. It considered that further progress would be greatly assisted by having agreed Definitions for Codex purposes. It recommended the Executive Committee that such definitions be elaborated as a matter of priority in accordance with the new Accelerated ("Fast Track") Procedure with a view to their adoption by the CAC at its 21st Session. The Committee proposed that the definitions contained in Appendix IX to the present report should be sent to governments for comments and also considered by other relevant Codex Committees. It emphasized that any definitions adopted by the Commission should be harmonised to the extent possible with those of other relevant international organizations, for example, the OIE.

9th Session of CCRVDF (December 1995) (ALINORM 97/31, para. 14)

At its 9th Session, at the request of the 21st Session of the Commission (1995) examined the report of the Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standards Issues (Geneva, Switzerland, 13-17 March 1995).

14. The Committee supported the incorporation of a science-based approach to risk analysis into its work, and agreed that a discussion paper would be developed under the direction of France, with assistance provided by Australia, Canada, the Netherlands, New Zealand, Norway and the United States, for consideration at its 10th Session. The paper should address the possible implementation of the recommendations of the FAO/WHO Expert Consultation of the Application of Risk Analysis to Food Standards Issues as they applied to the work of CCRVDF, and to consider initiatives undertaken by other Codex Committees.

10th Session of CCRVDF (October 1996) (ALINORM 97/31A, paras 9-13)

Following the decision of its 9th Session, the 10th Session of the Committee considered the paper by France to address the implementation of the Consultation's recommendations as they applied to the work of the Committee.

9. The Committee expressed its appreciation of the thorough analysis presented in the discussion paper. It noted that the development of risk analysis in Codex and in its work was an on-going process and that the analysis presented both a report of the current status and issues which needed to be addressed in the future. It concurred with the main conclusions of the paper, namely that the process of establishing MRLs for veterinary drugs incorporated various the stages of risk assessment very well, and that a number of elements relating to risk management were integrated. It noted that the recommendation made by the 1995 Joint FAO/WHO Expert Consultation to separate the risk assessment and the risk management processes was therefore not being currently followed in this process.

10. To the extent that it was possible to control strictly the conditions under which veterinary drugs were used, and food taken from treated animals could be collected, the Committee considered whether the results of the MRL-setting process was not so much as to evaluate a risk which would be socially acceptable, but to minimize risks associated with the presence of drug residues in food stuffs. However, the Committee further recognised the need to delineate more fully the risk assessment and the risk management of the process, and noted that government regulatory agencies and other played a major role in risk management of drug residues in foods.

11. The Committee identified several issues which required further attention, specifically:

- Better delineation of the respective roles of the Committee and JECFA;
- Improvement of transparency of the process;
- Recognition that the application of safety factors and other conventions to address uncertainty were not strictly scientifically based and therefore introduced an element of risk management into the risk assessment process;
- Consideration of the benefits of the use of veterinary drugs as well as risks, for animals as well as humans;
- Problems in relation to animal studies and the potential of using in vitro studies as alternative for such studies;
- Problems related to the generation of residue data for minor species, and;
- Problems related to old substances which had not been evaluated under modern criteria, but which were still in use in many countries, and substances on the so-called "inactive list".

12. The Committee agreed to refer its main findings to the Commission, but noting the forthcoming Expert Consultations of the Application of Risk management to Food safety Matters (Rome 28-31 January 1997) and on Food Consumption and Risk Assessment (Geneva, 10-14 February 1997), indicated its intention to circulate a revised paper for comments incorporating the issues raised at the present session and the outcome of these Consultations and of the Commission's deliberations. In the meantime, delegations were encouraged to send comments on the

discussion paper directly to the Delegation of France. The Committee welcomed the offer of the French Delegation to revise the document accordingly.

13. The Committee agreed to review developments in risk analysis at its next Session following consideration of this matter by the Commission.

11th Session of CCRVDF (September 1998) (ALINORM 99/31, paras 43-44)

At its 11th Session, the Committee considered the revised "Discussion paper on Risk Analysis in the Codex Committee on Residues of Veterinary Drugs in Foods" (CX/RVDF 98/4)

43. The revised paper was presented by Dr J. Boisseau (France). He noted that the paper had been expanded to take into account the recommendations of the FAO/WHO consultations, particularly those on risk management and risk communication. He reviewed the three elements of risk analysis as they pertain to this Committee and in particular, noted that issues related to risk assessment would require the development of risk assessment policies. In the interest of transparency, these policies should be made explicit.

44. Several delegations congratulated the French Delegation on its excellent work. Due to the late availability of the document, an in-depth discussion of the paper was not possible. The Committee agreed to append the document to its report (see Appendix IX) for circulation and comments, with the understanding that France would take the lead in revision of the paper on the basis of the above discussion and comments submitted for further consideration at its next meeting. The Delegations of the Netherlands, New Zealand, Sweden, the United Kingdom and the United States and representatives of Consumers International, COMISA, WHO and WHA agreed to assist France in this effort. In revising the paper, the Committee also requested that the document include specific risk assessment policy issues that may need to be addressed.

12th Session of CCRVDF (March 2000) (ALINORM 01/31, paras 15-19)

At its 12th Session, the Committee considered risk analysis principles and methodologies of the Codex Committee on Residues of Veterinary Drugs in Foods (CX/RVDF 00/3 "Overview and discussion on risk analysis by the 23rd Session of the Commission" and CX/RVDF 00/3, Add.1 "Risk Analysis Principles and Methodologies of the Codex Committee on Residues of Veterinary Drugs in Foods – Elaboration of a Risk Assessment Policy by the CCRVDF").

15. The Committee noted and welcomed the recommendation of the 23rd Session of the Commission in relation to principles of risk analysis addressed to the Codex Alimentarius Commission and its subsidiary bodies, governments, and FAO and WHO. Among those recommendations relevant to the work of this Committee, the Committee agreed that it would consider, pending the preparation of a discussion paper: (1) the development and application of risk analysis principles and methodologies appropriate to the specific mandate within the framework of the Action Plan; and (2) development of quality criteria for data used for risk assessment. It took note, for implementation as appropriate, of the recommendations regarding the appointment of a developing country(ies) as co-author(s) for position papers; basing risk assessment on global data including that from developing countries; taking into account the economic consequences and the feasibility of risk management options in developing countries; and consideration of acute aspects of dietary exposure to chemicals in foods. It also took note of the recommendations to increase interaction and communication between expert bodies and the Codex Committees.

16. The Delegation of France introduces the paper CX/RVDF 00/3-Add.1. It was stated that comments had been received on the text contained in Appendix IX of ALINORM 99/31 only from Consumers International and therefore the text had not been revised. The Delegation mentioned that

the Committee had not yet established risk assessment policy which was a component of risk management and the work should be done urgently on this issue. It was proposed that since the issue was very technical and complex, in order to facilitate discussion on the plenary, a drafting group should be formed to prepare a discussion paper containing solid recommendations regarding risk analysis principles and methodologies including risk assessment policy. For this purpose, the Delegation drew the attention of the Committee to existing reference documents of JECFA relevant to the issue.

17. A number of delegations supported the creation of a drafting group. Several delegation and one observer stated that the paper prepared for the last session contained useful information that should be used as a basis for further development.

18. A delegation stated that risk management was the function of Codex Committees and national governments, the leadership in this work should be taken by this Committee; and all efforts should be made to encourage developing countries to take part in the draft. Another delegation proposed that information should be requested from all concerned on subjects to be included in the paper in addition to what has been done by JECFA.

19. The Committee agreed that a drafting group (Australia, Brazil, Canada, Chile, France, Japan, Mexico, Netherlands, New Zealand, Philippines, Poland, Sweden, Switzerland, Thailand, United States, JECFA Secretariat, European Community, OIE, WHO, Consumers International and COMISA) led by France and Poland would prepare a discussion paper for government comments well before the next session of the Committee. In order to facilitate the drafting process, member countries were invited to provide comments and information relevant to the subject to France. It was mentioned that the drafting process should be accelerated by using modern communication technologies. It was noted that the process of drafting the paper should be as transparent as possible.

13th Session of CCRVDF (December 2001) (ALINORM 03/31, paras 65-70)

At its 13th Session, the Committee considered a document on Risk Analysis Principles and Methodologies of the Codex Committee on Residues of Veterinary Drugs in Foods (CX/RVDF 01/9) and noted the recommendation of the 24th Session of the Commission that relevant Codex committees should continue to develop and document the application of risk analysis in their work.

65. The Committee was also informed of the Commission request to FAO and WHO to convene a consultation to review the status and procedures of expert bodies and to develop recommendations for consideration by the Directors-General on additional ways to improve the quality, quantity and timeliness of scientific advice to the Commission. It was noted that this review would include the examination of increased coordination between the JECFA, JMPR and other groups devoted to microbiological contamination and biotechnology on matters including selection and establishment of a roster of experts for such bodies, including increased transparency in the process.

66. In presenting the Discussion Paper, the delegation of France noted that the document contained three major sections, namely: a background section describing the major elements of risk analysis and their relation to the mandates of CCRVDF and JECFA; Annex I – Establishment by CCRVDF of a Risk Assessment Policy for the Setting of Maximum Residue Limits for Veterinary Drugs in Foods; and, Annex II - Risk Management and Codex Procedures for Establishing MRLs of Veterinary Medicinal Products. The delegation of France noted that Annex I examined various aspects of risk assessment which need to be addressed in taking risk management decisions within the CCRVDF and contained a list of questions to JECFA to be answered at various steps of JECFA evaluation, including outstanding issues related to the harmonization of risk assessments between JECFA and JMPR as well as between CCRVDF and CCPR; the extrapolation of MRLs to minor species and the importance of criteria concerning the protection of public health and the promotion of

fair trading practices when prioritizing compounds for JECFA review. It was noted that Annex II contained four recommendations related to the uncertainty of whether or not a substance to be considered should be marketed or not; the importance of prioritizing compounds for reasons of public health protection as well as for the promotion of trade and the availability of a dossier for evaluation; the importance of the availability of JECFA reports in a timely manner; and, the elaboration of risk management principles and criteria.

67. The Committee confirmed that in undertaking its responsibilities related to risk analysis it was necessary to formulate a coherent risk assessment policy so that sound risk management decisions could be taken in the elaboration of MRLVDs and the scientific integrity of JECFA would be protected and for transparency. It was noted that notwithstanding the independence of JECFA, this would allow the Committee to take a full role in the consideration of JECFA evaluations and in this regard, it was suggested that Annex I could be examined at the next JECFA Meeting. It was noted that Annex I could provide the basis for the future development of a risk assessment policy which would facilitate discussions and relations with JECFA in the establishment of MRLVDs.

68. Although the Committee did not reach any final conclusion on Annex 1, it was decided to forward Annex I of the document to FAO and WHO, so that it would be taken into consideration in a joint project to update and consolidate principles and methodologies of risk assessment and that JECFA would review and comment back to the CCRVDF, with the understanding that these issues would be further considered by the CCRVDF at its next Session. It was noted that the review could greatly contribute to increased communication and transparency between risk assessors and managers and would help the Committee in defining risk assessment policies and risk management guidelines related to the establishment of MRLVDs.

69. The Committee generally agreed that risk management methodologies including policies for risk assessment and risk management, be drafted to address the needs of the Codex Alimentarius Commission pertaining to the activities of this Committee. The Committee concluded that the delegation of France, with the assistance of Australia, Brazil, Canada, Chile, China, Indonesia, Japan, Korea, Mexico, the Netherlands, New Zealand, Philippines, Poland, Sweden, Switzerland, Thailand, United States, CI, EC, FAO, IFAH, OIE and WHO, would elaborate an internal policy document on "Risk Management Methodologies, including Risk Assessment Policies, in the Codex Committee on Residues of Veterinary Drugs in Foods" considering Annex II of CX/RVDF 01/9 and the comments of JECFA on Annex I of CX/RVDF 01/9. It was agreed that the paper should address the written comments submitted as well as issues raised at the current meeting under agenda items 9, 11 and 13 that were relevant to risk analysis. The Committee agreed that the document should be circulated for comment and further consideration at its next meeting, and with the understanding that the policy document would remain as internal guidance to the CCRVDF.

70. It was further agreed that the drafting group would also consider risk management options for substances which were on the past agendas of JECFA but for which no ADI or MRLs had been recommended due to various reasons, including insufficient or lack of data or where no sponsor was identified.

14th Session of CCRVDF (March 2003) (ALINORM 03/31A, paras 91 and 94-96)

At its 14th Session, the Committee considered the revised discussion paper on risk management methodologies, including risk assessment policies (CX/RVDF 03/8) that described the mandate, the role of various parties with responsibilities in risk assessment and risk management and the steps of risk management in CCRVDF. The paper also provided practical recommendations to the questions raised by the CCRVDF regarding the need to accelerate the establishment of MRLVDs, the interactions between risk assessors and risk managers; the establishment of criteria and methods to propose temporary ADIs, and; the substances with no acceptable ADI and/or MRLs .

91. The Committee expressed general support for the document prepared by France as the recommendations adequately addressed issues related to the application of risk analysis policy, the efficiency of the work of CCRVDF and the proposal of Thailand. It was recommended to better specify the responsibilities of risk managers and risk assessors, their interactive mechanisms and the communication aspects in recommendations 3, 5, 6, and 7 and to highlight the primary purpose of protecting consumers health in the establishment of MRLVDs.

94. The Committee considered the further development of the discussion paper. Some delegations suggested to follow an approach similar to the Codex Committees on Pesticide Residues and on Food Additives and Contaminants and to consider the development of a dynamic document for internal use of the Committee and in consideration of the further development of specific guidelines for risk analysis.

95. The Committee agreed that a working group (lead by France, and with the assistance of Australia, Canada, China, Costa Rica, Italy, Korea, The Netherlands, New Zealand, Poland, Spain, Switzerland, Thailand, United Kingdom, United States, Consumers International, European Commission, FAO, IFAH, OIE and WHO) would prepare a revised version of the discussion paper on "Risk Management Methodologies, including Risk Assessment Policies in the Codex Committee on Residues of Veterinary Drugs in Foods" for circulation, additional comments and further consideration at its 15th Session. The Committee accepted the kind offer of the European Community to possibly host a meeting of the working group in Brussels to discuss the further development of the document.

96. The Committee agreed that the revised document should specifically address the issue of substances with no ADI and/or MRL, should take account of the above discussion, the written comments submitted at the current meeting and the comments of the 60th meeting of JECFA on Annex I of CX/RVDF 01/9.

15th Session of CCRVDF (October 2004) (ALINORM 05/28/31, paras 141-153)

At its 15th Session, the Committee considered and reviewed the internal policy document on risk management methodologies, including risk assessment policies (CX/RVDF 04/15/08), which was prepared by the drafting group on the basis of the document presented at its previous session and the comments provided by JECFA.

141. The Committee had an extensive discussion on the need for communication strategies for risk analysis. Several delegations stressed the need for better communication between risk assessors and risk managers. The Observer from Consumers International expressed the view that communication with the public was an essential aspect of risk analysis in order to ensure public confidence in the process. The Delegation of the European Community expressed the view that the document should concentrate on communication between risk assessors and risk managers and that communication with the public might be better addressed by national governments.

142. The JECFA Secretariat highlighted the importance of adequate risk communication, especially if new procedures were developed for risk analysis of veterinary drugs, and in the case of substances that currently had no ADI or MRLs.

143. The Committee agreed that risk communication strategies should be further considered in the development of the document, and noted that the section on Risk Communication in the *Working Principles for Risk Analysis in the Framework of the Codex Alimentarius* could be taken into account in the process.

144. In reply to a question on risk assessment procedures, the Representatives of FAO and WHO informed the Committee that the procedures of JECFA and JMPR were in the process of review and would be available upon completion of the Joint FAO/WHO Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Foods, scheduled for 2005. It was noted that what constitute Good Veterinary Practices, as applied to milk withdrawal time, should be considered a component of the risk management process.

Risk Management in the CCRVDF

Identification of a Food Safety Problem

145. The Committee noted that to be consistent with the mandate of the Codex Alimentarius, food safety needs and public health concerns (paragraphs 11 and 13), trade issues of relevance for governments should also be identified.

146. The Committee noted the written comments of Argentina, which was not present at the meeting, concerning intellectual property in paragraph 12. In this respect, the Secretariat informed the Committee that the *Working Principles for Risk Analysis in the Framework of the Codex Alimentarius* (paragraph 6) addressed the issue of confidentiality as related to the accessibility of documentation.

147. Some delegations and the Observer from IFAH expressed the view that what constituted "documentation" for the purpose of risk analysis should be more clearly defined and that intellectual property issues should be further clarified.

148. The JECFA Secretariat recalled that procedures existed to ensure confidentiality of proprietary information in JECFA but that toxicological information was published in the report of the risk assessment.

149. The Committee agreed that a risk assessment policy should be established and the issue of "drugs with a long history of use" should be addressed, and noted that this was related to the establishment of lists of substances of interest to member governments that would be considered in the discussion on priorities (see also Agenda Item 12).

150. Regarding the provisions on the risk profile in paragraph 16, the JECFA Secretariat clarified that the qualitative risk profile should be provided by the delegation that initially proposed the substance for evaluation, in reply to the questionnaire sent to request comments on priorities.

Monitoring and review of the decisions taken

151. The Committee agreed that a list of veterinary drugs for which no ADI or MRL had been established should be compiled and discussed whether a policy should be established concerning the status of that list but did not come to a conclusion. Some delegations pointed out that the absence of a MRL did not directly relate to a food safety issue, as in some cases MRLs had not been established, due to insufficient data or lack of data for minor species. In reply to a question, the JECFA Secretariat indicated that a Summary of JECFA Evaluations of Veterinary Drugs Residues from the 32nd Meeting to the present (62nd Meeting) had been published in the document FAO FNP 41/16. This document also contains a list of compounds which have been evaluated by JECFA but for which an ADI and/or MRL was not recommended.

152. The Committee recalled the request of the Commission for Codex Committees to complete their work on guidelines on risk analysis in their respective areas and agreed that the discussion paper should be redrafted as a working document for inclusion in the Procedural Manual, with a view to its

finalization at the next session. The Committee agreed that the document was being developed in response to a direct request of the Commission and did not need to go through the Step Procedure.

153. The Committee agreed that the document should be redrafted by the Delegation of France with the assistance of a working group¹⁵ taking into account the written comments, the discussion at the present session, and the recommendations of the Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL, where applicable. It requested the Working Group to submit the revised version by September 2005, for comments and consideration by the next session.

16th Session of CCRVDF (May 2006) (ALINORM 06/29/31, para. 111 and Appendices VII and IX)

At its 16th Session, the Committee considered the revised paper on risk management methodologies (CX/RVDF 06/16/10) which included two texts on: Risk Analysis Methodologies in the Codex Committee on Residues of Veterinary Drugs in Foods and Risk Assessment Policy for the Setting of MRLs in Food.

111. The Committee agreed to forward the renamed Risk Analysis Principles applied by the Codex Committee on Residues of Veterinary Drugs in Foods and the Risk Assessment Policy for the Setting of MRLs in Food to the Codex Alimentarius Commission, through the Codex Committee on General Principles, for adoption and inclusion in the Codex Procedural Manual (see Appendices VIII and IX).

ALINORM 06/29/31, Appendix VIII

PROPOSED DRAFT
RISK ANALYSIS PRINCIPLES APPLIED BY THE CODEX COMMITTEE
ON RESIDUES OF VETERINARY DRUGS IN FOODS
(for inclusion in the Codex Procedural Manual)

1. PURPOSE – SCOPE

1. The purpose of this document is to specify Risk Analysis Principles applied by the Codex Committee on Residues of Veterinary Drugs in Foods.

2. PARTIES INVOLVED

2. The *Working Principles for Risk Analysis for application in the framework of the Codex Alimentarius*¹⁶ has defined the responsibilities of the various parties involved. The responsibility for providing advice on risk management concerning residues of veterinary drugs lies with the Codex Alimentarius Commission (CAC) and its subsidiary body, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRDVF), while the responsibility for risk assessment lies primarily with the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

3. According to its mandate, the responsibilities of CCRVDF regarding veterinary drug residues in food are:

¹⁵ Australia, Burkina Faso, Brazil, Canada, China, Colombia, Costa Rica, European Community, Japan, Korea, Malaysia, Netherlands, Switzerland, Sweden, Thailand, United States, ALA, CI, IFAH, OIE, and OIRSA

¹⁶ Codex Procedural Manual, 15th Edition page 101 (English version).

- (a) to determine priorities for the consideration of residues of veterinary drugs in foods;
 - (b) to recommend MRLs for such veterinary drugs;
 - (c) to develop codes of practice as may be required;
 - (d) to consider whether available methods of sampling and analysis for the determination of veterinary drug residues in foods.
4. CCRVDF shall base its risk management recommendations to the Codex Alimentarius Commission (CAC) on JECFA's risk assessments of veterinary drugs in relation to proposed MRLs.
5. CCRVDF is primarily responsible for recommending risk management proposals for adoption by the Codex Alimentarius Commission (CAC).
6. JECFA is primarily responsible for providing independent scientific advice, the risk assessment, upon which CCRVDF base their risk management decisions. It assists the CCRVDF by evaluating the available scientific data on the veterinary drug prioritised by CCRVDF. JECFA also provides advice directly to FAO and WHO and to Member governments.
7. Scientific experts from JECFA are selected in a transparent manner by FAO and WHO under their rules for expert committees on the basis of the competence, expertise, experience in the evaluation of compounds used as veterinary drugs and their independence with regard to the interests involved, taking into account geographical representation where possible.

3. RISK MANAGEMENT IN CCRVDF

8. Risk management should follow a structured approach including:
- preliminary risk management activities;
 - evaluation of risk management options; and
 - monitoring and review of decisions taken.
9. The decisions should be based on risk assessment, and take into account, where appropriate, other legitimate factors relevant for the health protection of consumers and for fair practices in food trade, in accordance with the *Criteria for the Consideration of the Other Factors Referred to in the Second Statement of Principles*¹⁷.

3.1 PRELIMINARY RISK MANAGEMENT ACTIVITIES

10. This first phase of risk management covers:
- Establishment of risk assessment policy for the conduct of the risk assessments;
 - Identification of a food safety problem;
 - Establishment of a preliminary risk profile;
 - Ranking of the hazard for risk assessment and risk management priority;

¹⁷ Codex Procedural Manual, 15th Edition page 159 (English version)

- Commissioning of the risk assessment; and
- Consideration of the result of the risk assessment.

3.1.1 Risk Assessment Policy for the Conduct of the Risk Assessment

11. The responsibilities of CCRVDF and JECFA and their interactions along with core principles and expectations of JECFA evaluations are provided in *Risk Assessment Policy for the Setting of MRLs in Food*, established by the Codex alimentarius Commission.

3.1.2 Identification of a Food Safety Problem (establishment of the priority list)

12. CCRVDF identifies, with the assistance of Members, the veterinary drugs that may pose a consumer safety problem and/or have a potential adverse impact on international trade. CCRVDF establishes a priority list for assessment by JECFA.

13. In order to appear on the priority list of veterinary drugs for the establishment of a maximum residue limit (MRL), the proposed veterinary drug shall meet some or all of the following criteria:

- A Member has proposed the compound for evaluation;
- A Member has established good veterinary practices with regard to the compound;
- The compound has the potential to cause public health and/or international trade problems;
- It is available as a commercial product; and
- There is a commitment that a dossier will be made available.

14. The CCRVDF takes into account the protection of confidential information in accordance with WTO rules article 39, and makes every effort to encourage the willingness of sponsors to provide data for JECFA assessment.

3.1.3 Establishment of a Preliminary Risk Profile

15. Member(s) request(s) the inclusion of a veterinary drug on the priority list. The available information for evaluating the request shall be provided either directly by the Member(s) or by the sponsor. A preliminary risk profile shall be developed by the Member(s) making the request, using the template presented in the ANNEX.

16. The CCRVDF considers the preliminary risk profile and makes a decision on whether or not to include the veterinary drug in the priority list.

3.1.4 Ranking of the Hazard for Risk Assessment and Risk Management Priority

17. The CCRVDF establishes an ad-hoc Working Group open to all its Members and observers, to make recommendations on the veterinary drugs to include into (or to remove from) the priority list of veterinary drugs for the JECFA assessment. The CCRVDF considers these recommendations before agreeing on the priority list, taking into account pending issues such as temporary Acceptable Daily Intakes (ADIs) and/or MRLs. In its report, the CCRVDF shall specify the reasons for its choice and the criteria used to establish the order of priority.

18. Prior to development of MRLs for new veterinary drugs not previously evaluated by JECFA, a proposal for this work shall be sent to the Codex Alimentarius Commission with a request for approval as new work in accordance with the Procedures for the Elaboration of Codex Standards and Related Texts.¹⁸

3.1.5 Commissioning of the Risk Assessment

19. After approval by the Codex Alimentarius Commission of the priority list of veterinary drugs as new work, the CCRVDF forwards it to the JECFA with the qualitative preliminary risk profile as well as specific guidance on the CCRVDF risk assessment request. JECFA, WHO and FAO experts then proceed with the assessment of risks related to these veterinary drugs, based on the dossier provided and/or all other available scientific information.

3.1.6 Consideration of the Result of the Risk Assessment

20. When the JECFA risk assessment is completed, a detailed report is prepared for the subsequent session of the CCRVDF for consideration. This report shall clearly indicate the choices made during the risk assessment with respect to scientific uncertainties and the level of confidence in the studies provided.

21. When the data are insufficient, JECFA may recommend temporary MRL on the basis of a temporary ADI using additional safety considerations¹⁹. If JECFA cannot propose an ADI and/or MRLs due to lack of data, its report should clearly indicate the gaps and a timeframe in which data should be submitted, in order to allow Members to make an appropriate risk management decision.

22. The JECFA assessment reports related to the concerned veterinary drugs should be made available in sufficient time prior to a CCRVDF meeting to allow for careful consideration by Members. If this is, in exceptional cases not possible, a provisional report should be made available.

23. The JECFA should, if necessary, propose different risk management options. In consequence, JECFA should present, in its report, different risk management options for CCRVDF to consider. The reporting format should clearly distinguish between the risk assessment and the evaluation of the risk management options.

24. The CCRVDF may ask JECFA any additional explanation.

25. Reasons, discussions and conclusions (or the absence thereof) on risk assessment should be clearly documented, in JECFA reports, for each option reviewed. The risk management decision taken by CCRVDF (or the absence thereof) should also be fully documented.

3.2 EVALUATION OF RISK MANAGEMENT OPTIONS

26. The CCRVDF shall proceed with a critical evaluation of the JECFA proposals on MRLs and may consider other legitimate factors relevant for health protection and fair trade practices in the framework of the risk analysis. According to the 2nd statement of principle, the criteria for the consideration of other factors should be taken into account. These other legitimate factors are those agreed during the 12th session of the CCRVDF²⁰ and subsequent amendments made by this Committee.

¹⁸ Codex Procedural Manual, 15th Edition pages 19-30 (English version).

¹⁹ Codex Procedural Manual, 15th Edition page 45 (English version).

²⁰ See Report of the 12th session of the CCRVDF ALINORM 01/31 para 11.

27. The CCRVDF either recommends the MRLs as proposed by JECFA, modifies them in consideration of other legitimate factors, considers other measures or asks JECFA for reconsideration of the residue evaluation for the veterinary drug in question.

28. Particular attention should be given to availability of analytical methods used for residue detection.

3.3 MONITORING AND REVIEW OF THE DECISIONS TAKEN

29. Members may ask for the review of decisions taken by the Codex Alimentarius Commission. To this end, veterinary drugs should be proposed for inclusion in the priority list. In particular, review of decisions may be necessary if they pose difficulties in the application of the *Guidelines for the Establishment of a Regulatory Program for the Control of Veterinary Drug Residues in Foods*.

30. CCRVDF may request JECFA to review any new scientific knowledge and other information relevant to risk assessment and concerning decisions already taken, including the established MRLs.

31. The risk assessment policy for MRL shall be reconsidered based on new issues and experience with the risk analysis of veterinary drugs. To this end, interaction with JECFA is essential. A review may be undertaken of the veterinary drugs appearing on prior JECFA agendas for which no ADI or MRL has been recommended.

4. RISK COMMUNICATION IN THE CONTEXT OF RISK MANAGEMENT

32. In accordance with the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius*²¹, the CCRVDF, in cooperation with JECFA, shall ensure that the risk analysis process is fully transparent and thoroughly documented and that results are made available in a timely manner to Members. The CCRVDF recognises that communication between risk assessors and risk managers is critical to the success of risk analysis activities.

33. In order to ensure the transparency of the assessment process in JECFA, the CCRVDF provides comments on the guidelines related to assessment procedures being drafted or published by JECFA.

ANNEX

TEMPLATE FOR INFORMATION NECESSARY FOR PRIORITIZATION BY CCRVDF

Administrative information

1. Member(s) submitting the request for inclusion
2. Veterinary drug names
3. Trade names
4. Chemical names
5. Names and addresses of basic producers

²¹ Codex Procedural Manual, 15th Edition page 161 (English version).

Purpose, scope and rationale

6. Identification of the food safety issue (residue hazard)
7. Assessment against the criteria for the inclusion on the priority list

Risk profile elements

8. Justification for use
9. Veterinary use pattern
10. Commodities for which Codex MRLs are required

Risk assessment needs and questions for the risk assessors

11. Identify the feasibility that such an evaluation can be carried out in a reasonable framework
12. Specific request to risk assessors

Available information²²

13. Countries where the veterinary drugs is registered
14. National/Regional MRLs or any other applicable tolerances
15. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available

Timetable

16. Date when data could be submitted to JECFA

ALINORM 06/29/31, Appendix IX

***PROPOSED DRAFT
RISK ASSESSMENT POLICY FOR THE SETTING OF MRLS IN FOOD
(for inclusion in the Codex Procedural Manual)***

ROLE OF JECFA

1. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an independent scientific expert body convened by both Director Generals of FAO and WHO according to the rules

²² When preparing a preliminary risk profile, Member(s) should take into account the updated data requirement, to enable evaluation of a veterinary drug for the establishment of an ADI and MRLs, published by JECFA.

of both organizations, charged with the task to provide scientific advice on veterinary drug residues in food.

2. This annex applies to the work of JECFA in the context of Codex and in particular as it relates to advice requests from CCRVDF

- (a) JECFA provides CCRVDF with science-based risk assessments conducted in accordance with the *Statements of principles relating to the role of food safety risk assessment*²³ and incorporating the four steps of risk assessment. JECFA should continue to use its risk assessment process for establishing ADIs and proposing MRLs.
- (b) JECFA should take into account all available scientific data to establish its risk assessment. It should use available quantitative information to the greatest extent possible and also qualitative information.
- (c) Constraints, uncertainties and assumptions that have an impact on the risk assessment need be clearly communicated by JECFA.
- (d) JECFA should provide CCRVDF with information on the applicability, public health consequences and any constraints of the risk assessment to the general population and to particular sub-populations and, as far as possible, should identify potential risks to specific group of populations of potentially enhanced vulnerability (e.g. children).
- (e) Risk assessment should be based on realistic exposure scenarios.
- (f) When the veterinary drug is used both in veterinary medicine and as a pesticide, a harmonised approach between JECFA and JMPR should be followed.
- (g) MRLs, that are compatible with the ADI, should be set for all species based on appropriate consumption figures. When requested by CCRVDF, extension of MRLs between species will be considered if appropriate data are available.

DATA PROTECTION

3. Considering the importance of intellectual property in the context of data submission for scientific evaluation, JECFA has established procedures to cover the confidentiality of certain data submitted. These procedures enable the sponsor to declare which data is to be considered as confidential. The procedure includes a formal consultation with the sponsor.

EXPRESSION OF RISK ASSESSMENT RESULTS IN TERMS OF MRLS

4. MRLs have to be established for target animal tissues (e.g. muscle, fat, or fat and skin, kidney, liver), and specific food commodities (e.g. eggs, milk, honey) originating from the target animals species to which a veterinary drug can be administered according to good veterinary practice.

5. However, if residue levels in various target tissues are very different, JECFA is requested to consider MRLs for a minimum of two. In this case, the establishment of MRLs for muscle or fat is preferred to enable the control of the safety of carcasses moving in international trade.

²³ Codex Procedural Manual 15th Edition page 161 (English version).

6. When the calculation of MRLs to be compatible with the ADI may be associated with a lengthy withdrawal period, JECFA should clearly describe the situation in its report.

ANNEX 8

DEFINITIONS OF RISK ANALYSIS TERMS RELATED TO FOOD SAFETY²⁴

Hazard: A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect.

Risk: A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food.

Risk Analysis: A process consisting of three components: risk assessment, risk management and risk communication.

Risk Assessment: A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization.

Risk Management: The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.

Risk Communication: The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.

Risk Assessment Policy: Documented guidelines on the choice of options and associated judgements for their application at appropriate decision points in the risk assessment such that the scientific integrity of the process is maintained.

Risk Profile: The description of the food safety problem and its context.

Risk Characterization: The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.

Risk Estimate: The quantitative estimation of risk resulting from risk characterization.

Hazard Identification: The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods.

Hazard Characterization: The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are obtainable.

Dose-Response Assessment: The determination of the relationship between the magnitude of exposure (dose) to a chemical, biological or physical agent and the severity and/or frequency of associated adverse health effects (response).

²⁴ Procedural Manual of the Codex Alimentarius Commission (15th Edition).

Exposure Assessment: The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant.

Food Safety Objective (FSO): The maximum frequency and/or concentration of a hazard in a food at the time of consumption that provides or contributes to the appropriate level of protection (ALOP).

Performance Criterion (PC): The effect in frequency and/or concentration of a hazard in a food that must be achieved by the application of one or more control measures to provide or contribute to a PO or an FSO.

Performance Objective (PO): The maximum frequency and/or concentration of a hazard in a food at a specified step in the food chain before the time of consumption that provides or contributes to an FSO or ALOP, as applicable.

ANNEX 9

RECOMMENDED INTERNATIONAL CODE OF PRACTICE FOR CONTROL OF THE USE OF VETERINARY DRUGS

CAC/RCP 38-1993

INTRODUCTION

1. This Code sets out guidelines on the prescription, application, distribution and control of drugs used for treating animals, preserving animal health or improving animal production. The Code is intended to apply to all States which are members of the organizations under whose auspices the project is being developed and to contribute towards the protection of public health.

2. Good practice in the use of veterinary drugs (GPVD), as defined by the CCRVDF, is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions. The maximum residue limit for veterinary drugs (MRLVD) may be reduced to be consistent with good practice in the use of veterinary drugs. The MRLVD is based on the type and amount of residue considered to be without toxicological hazard for human health while taking into account other relevant public health risks as well as food technological aspects.

3. Veterinary products (including premixes for manufacture of medicated feedingstuffs) used in food producing animals should be administered (or incorporated into feed) in compliance with the relevant product information approved by national authorities and/or in accordance with a prescription and/or instruction issued by a qualified veterinarian.

REGISTRATION AND DISTRIBUTION - GENERAL REQUIREMENTS

4. All medicinal products (i.e., all veterinary therapeutic products) and medicinal premixes for inclusion in animal feeds should comply with the OIE Code of Practice for the Registration of Veterinary Drugs and be registered with the national authority. Products should only be distributed through veterinarians, registered wholesalers, pharmacists or other retail outlets permitted by national laws and regulations. Records of products taken into and leaving the premises should be maintained. Storage and transport conditions must conform to the specifications on the label, in particular those concerning temperature, humidity, light, etc.

RESPONSIBILITY OF THE VETERINARIAN AND OF OTHERS AUTHORIZED TO HANDLE OR ADMINISTER MEDICINES - GENERAL PROVISIONS

5. Whenever veterinary drugs are handled or administered it is important to recognize that potentially hazardous effects may occur in animals or in human operators. When the administration of a medicine is not under direct veterinary supervision, it is therefore essential that, after the diagnosis, clear instructions should be provided on dose and methods of use, taking account of the competence of the user performing the work and ensuring that the correct calculation of, and the importance of adhering to, withdrawal periods is fully understood. It is similarly important to ensure that the farm facilities and management systems employed enable the withdrawal periods to be observed.

6. In determining treatments, it is necessary to ensure that an accurate diagnosis is obtained and be guided by the principles of maximum effectiveness combined with minimum risk. Specific

treatments should be presented using as few products as possible and avoiding the use of combination products, unless pharmacological advantages have been demonstrated.

7. Veterinarians should keep in mind that uncontrolled and unlimited use of medicinal products may lead to the accumulation of undesirable residues in the animals treated and in the environment, and that the continuous use of anticoccidial, antibacterial or anthelmintic products may favour the development of resistance. It is the responsibility of the veterinarian or other authorized persons to draw up programmes of preventive medicine for the farmer and to stress the importance of sound management and good husbandry procedures in order to reduce the likelihood of animal diseases. Every effort should be made to use only those drugs known to be effective in treating the specific disease.

8. The veterinarian should stress the need for diseased animals to be segregated from healthy animals and treated individually where possible.

9. Beyond his responsibility for advice on measures that will reduce the incidence of disease and for controlling it when it arises, the veterinarian is also responsible for taking the welfare of livestock fully into account.

INFORMATION OF VETERINARY DRUGS

10. Product information considered essential by the national authority to ensure the safe and effective use of veterinary medicinal products must be made available in the form of labelling, data sheets or leaflets. Information on dosage schedules should be complemented by instructions on dose-related recommended withdrawal periods, interactions, contra-indications and any other constraints on the use of the product including any precautions regarded as necessary.

AMOUNTS TO BE SUPPLIED

11. Medicines should not be supplied in excess of immediate requirements as this may lead to incorrect use or to deterioration of the products.

PREPARATION OF MEDICINES

12. The preparation of medicines and medicated feeds should be undertaken by suitably trained personnel, using appropriate techniques and equipment.

ADMINISTRATION OF MEDICINES

13. Special attention should be paid to the prescription and to using the correct dosage, site and route of administration. Note should be taken of all warning statements, interactions and contra-indications for use (in particular any incompatibility with other medicinal products). It is important not to use the product once the expiry date has passed.

14. In disease circumstances where no authorized product exists or certain indications or target species are not provided for in the product literature, the veterinarian can on his own responsibility or with advice from the manufacturer have recourse to other licensed products or off label use. Administration of products in this manner, however, may have unpredictable side effects and give rise to unacceptable residue levels. Veterinarians should therefore only embark on such uses, especially in food-producing animals, after the most careful consideration of the needs of the disease situation. Under these circumstances, a significantly extended withdrawal time should be assigned for drug withdrawal prior to marketing milk, meat or eggs. The veterinarian is responsible for providing written instructions on the use and withdrawal times for all medicines used off label. Off label use by

persons other than veterinarians must not be permitted except when such use is conducted or permitted under the supervision or prescription of the veterinarian.

15. To avoid the presence of unacceptable residues in meat or other by-products of animal origin, it is essential that the livestock owner adheres to the withdrawal period laid down for each product and dose regime or to a suitably lengthy withdrawal period, prescribed by a veterinarian, where none is specified. Full instructions should be given as to how this period is to be observed, including the use of on site residue detection methods where applicable and on the disposal of any animals slaughtered during treatment or before the end of the withdrawal period. If animals are sold before the end of the withdrawal period, the buyer must be informed.

RECORD KEEPING REQUIREMENTS

16. The veterinarian and/or the livestock owner or other authorized persons should keep a record of the products used, including the quantity, the date of administration and the identity of animals on which the medicines were used. Each record should be kept for at least two years, and presented when required by the competent authorities.

WITHDRAWAL OF VETERINARY DRUGS

17. Where the veterinarian or other authorized person suspects that unexpected adverse reactions involving illness, abnormal clinical signs, or death in animals, or any harmful effects in persons administering veterinary medicines have been associated with a veterinary product, they should be reported to the appropriate national authority. Regular feed-back or information to veterinarians and manufacturers on suspected adverse reactions should be encouraged.

STORAGE OF VETERINARY DRUGS

18. Veterinary products should be correctly stored in accordance with label instructions. It should be kept in mind that storage temperatures are critical for some medicines, while exposure to light or to moisture can damage others. Prescription medicines should be separated from non-prescription medicines.

19. All veterinary products should be stored in secure premises and kept under lock and key where practicable and out of reach of children and animals.

DISPOSAL OF VETERINARY DRUGS

20. Veterinary drugs remaining after treatment has been completed must be disposed of safely according to labelled instructions. Partially used containers should not be retained for future use. Unused drugs beyond their expiry date may however be returned to the vendor if there is an agreement to that effect. Where administration of medicines is not under direct veterinary supervision, users should be advised about correct disposal measures, e.g., to reduce potential contamination of the environment.

DISPOSAL AND CLEANING OF DRUG ADMINISTRATION EQUIPMENT

21. Disposable equipment used for administration of veterinary drugs must be disposed of safely and in accordance with correct disposal procedures. Where drugs are not administered under veterinary supervision, disposable syringes, needles, catheters and other drug administration equipment should, wherever practicable, be returned to the supplying veterinary practice to ensure correct disposal procedures.

22. Cleaning of equipment used for the administration of veterinary drugs must be carried out in a manner that ensures the safety of human health and the environment. After cleaning, any material containing residues of the veterinary drug should be disposed of using the same procedures that apply to disposal of the drug itself.

ANNEX 10

CODEX GUIDELINES FOR THE ESTABLISHMENT OF A REGULATORY PROGRAMME FOR CONTROL OF VETERINARY DRUG RESIDUES IN FOODS

CAC/GL 16-1993

Governments need regulatory control programmes to ensure their citizens of a safe and wholesome food supply. Specifications of a residue control programme are determined by the importance of the various health risks that could be incurred by consumers of products derived from animal food products.

One type of risk may occur if meat is handled and consumed from animals excessively contaminated with microorganisms or toxins that could affect the health of consumers. This type of health risk can be minimized by establishing meat inspection programmes that emphasize appropriate and provide specific procedures on how to recognize the signs of disease in food producing animals.

Another kind of risk can occur if food animals have been raised using veterinary drugs or pesticides in an inappropriate manner. The improper use of such chemicals can result in unsafe residues of these substances in food derived from the treated animals. The safety of the human food requires a full scientific evaluation of the relative hazard as well as quantity of a drug residue remaining in the tissues of treated livestock and poultry when used according to good veterinary practices, and a systematic set of procedures that will ensure effective control of such residues in human food.

In addition to the health protection benefits in having an effective residue control programme, a country with such a programme has the capability to participate in the community of food trading nations with greater confidence. This is because an effective residue control programme can also serve as the foundation for certifying the safety of the country's exported food products, as well as provide assurance of safety of such products imported into the country.

When establishing a programme for control of residues in foods, it is important to distinguish between the notion of "unbiased statistical sampling", where the samples are obtained from animals that are presented for inspection, and the notion of "biased or directed sampling", where samples are obtained from suspect food products. The purpose of unbiased statistical sampling is to determine the frequency of occurrence of contaminated products among those presented for inspection.

Samples are taken at random from food considered safe, and it is not necessary to retain these food products while waiting for the results of analytical testing. The sampling plan is determined beforehand, using statistical rules to ensure that the results are representative of the overall quality of the product(s) under consideration. The results may be used to certify the exported food products are in compliance with Codex MRLVDs. Conversely, directed sampling focuses on food products suspected of having residue concentrations that exceed the maximum residue limits. The food products are detained while waiting for results of laboratory testing, and are not released for human consumption should test results be unfavourable. The number of samples to be taken during the year for directed sampling may not, by definition, be predetermined. The results of directed sampling do not have statistical representativeness.

In establishing an effective residue control programme, a country should first establish a comprehensive system for determining the safety of veterinary drugs. This may be accomplished, for example, through an organization with suitable technical expertise and administrative authority. Veterinary drugs may be approved taking into consideration several relevant criteria, among which

will be the safety evaluation of the veterinary drug for animals and for human food consumption. The scientific evaluation of the safety of veterinary drugs is a long and rigorous task, that, perhaps, may not be necessary to perform in each country, especially in developing countries. Evaluation could be performed by the interested country, using the technical expertise of international organizations such as the Joint FAO/WHO Expert Committee on Food Additives (for veterinary drugs), or the technical evaluation results in other countries having an acceptable, technically qualified safety assessment organizations.

To establish an effective programme for the control of residues of veterinary drugs in food, a country should include but not necessarily be limited to the following items:

1. Establishing the regulatory authority responsibility for implementing inspection programmes and laboratory analyses.
2. Elaborating an integrated inspection programme, including a residue control programme for the inspection of foods. The organization in charge of implementing this inspection programme should be granted the authority to take all the steps necessary to control products when residues exceed the maximum residue limits established for a food commodity.
3. Compiling a register of veterinary drugs and/or pure chemical; substances used in the country, including the products manufactured in the country and those products that are imported into the country.
4. Elaborating regulations concerning the distribution of veterinary drugs as a whole, providing for procedures for the authorized sale, manufacture, distribution and use of such products.
5. Elaborating procedures for determining the safety and efficacy of veterinary drugs in animals and residues in food from use of such veterinary drugs. This should include describing procedures for determining maximum residue limits for veterinary drugs in food and procedures for analysis of test samples intended to verify compliance with those limits.
6. Establishing procedures for sampling food products of animal origin, indicating the specific drug residues of greatest health concern, the number of samples to be taken for unbiased statistical sampling, and the nature of the tissue and quantity of sample to be taken. Procedures for sampling for residue control in a country may be required for certain substances for purposes other than the enforcement of MRLVDs. These analyses, for example, come within the scope of exploratory surveys for determining residues in foods where unapproved substances may be used in food producing animals or poultry. This type of data is essential to provide a residue control programme the flexibility necessary to be adapted to national needs.
7. Selecting the methods of analysis to be used. As an initial step, a residue control programme should include screening methods. The use of these methods should not require investment in complex laboratory instrumentation nor in costly reagents or personnel training, and should provide analysis of samples in a cost effective manner. Screening methods are generally defined as qualitative or semi-quantitative methods of analysis that detect the presence of a substance at a concentration that is equal to or lower than the maximum residue limits. A positive result indicates the possibility that the maximum residue limit has been exceeded. Additional testing measures should be required, as determined by the objectives set forth in a country's residue control programme, to verify or confirm the results of screening methods.
8. Implementing a quality assurance programme to assure the highest quality results for methods of analysis. Such a programme will assure regulatory control authorities that the methods used will

give reliable results that are compatible with the MRLVD or within the limits established by national regulations.

9. Developing an educational programme(s) for producers and veterinarians providing instruction in the proper use of veterinary drugs, and encouraging the use of preventive measure to reduce the occurrence of residues in food animals and poultry.

For determining maximum residue limits, the Joint FAO/WHO Expert Committee on Food Additives (for veterinary drugs) may constitute a useful resource for obtaining these data.

10. Specific details concerning the establishment of a regulatory programme for control of veterinary drug residues in foods, as based on the above general principles, are attached to these guidelines as follows:

PART 1:	Sampling for the Control of Residues of Veterinary Drugs in Foods
Appendix A:	Sampling for the Control of Veterinary Drug Residues in Meat and Poultry Products
Appendix B:	Sampling for the Control of Veterinary Drug Residues in Fish, Milk, and Egg Products
Appendix C:	Sampling for the Control of Veterinary Drug Residues in Honey
PART 2:	General Considerations on Analytical Methods for Residue Control
PART 3:	Attributes of Analytical Methods for Residues of Veterinary Drugs in Foods

PART I

SAMPLING FOR THE CONTROL OF RESIDUES OF VETERINARY DRUGS IN FOODS

1. INTRODUCTION

1.1 Basis for the Sampling Principle

The Codex Alimentarius Commission has decided that recommended sampling procedures for food additives, pesticide residues and residues of veterinary drugs in food are exempted from the general sampling procedures of food commodities developed by the Codex Committee on Methods of Analysis and Sampling - Normal Practice. That committee's work is concerned mainly with sampling procedures for the visible and measurable qualities and attributes of various commodities and foods; sampling to determine whether standards of identity and composition have been met and to measure traditional attributes of quality, such as dust and moisture content in grain. The Codex Committees that are responsible for establishing permitted levels of regulated added substances - food additives, pesticides, veterinary drugs in food, have been given authority to prepare their own recommendations for methods of analysis and sampling. In this regard, the Codex Committee on Residues of Veterinary Drugs in Foods established an *Ad Hoc* Working Group on Methods of Analysis and Sampling at its first meeting.

1.2 General Principles

Sampling for analytical testing is only one element of a country's residue control programme and, by itself, cannot accomplish the entire objective of protecting public health. Sampling is a tool used as part of the system for developing information to determine if a supply of foodstuffs meets public health requirements, in this case, that the concentration of veterinary drug residues are within specified limits.

Sampling has varying purposes and statistical parameters. This guideline discusses the various objectives which sampling may address and provides technical guidance to be applied for sampling products within the terms of reference of this Codex Committee. By using Codex standards, including agreed upon sampling methods, member countries can comply with Article III of the General Agreement on Tariffs and Trade.

In sampling for residues of an added, regulated substance such as a veterinary drug, it is important to sample as near as possible to where animals raised for food are cared for and slaughtered in herds or flocks. The most meaningful sampling for tissue residues will occur in conjunction with slaughter. For other food products within the scope of this Committee, such as honey, the most meaningful sampling for residues will occur at the time of collection, prior to commingling of samples from different producers.

Sampling at an abattoir in conjunction with slaughter of a herd or flock or with preliminary slaughter of a small number of test animals or birds, may involve testing samples drawn from live animals or birds. In these situations, analyses performed on tissues drawn from test animals or body fluids from live animals may provide test results for an inspector before a herd or flock is presented for slaughter or shipment. Analyses associated with pre-slaughter must be designed to prevent subsequent administration of drugs. In a like manner, for processed foods such as might be obtained from fish or honey, any sampling and testing must be designed to prevent subsequent administration of drugs. When body fluids are used for residue testing, care must be taken to have established tissue-fluid relationships between the analytic results in these fluids and results in tissues where the MRLVDs are established.

Shortly after slaughter or after appropriately harvesting the principle food products, these products may be commingled to an extent that it destroys the possibility of drawing a representative sample. Samples for fresh meat or poultry or fresh chilled meat or poultry may be drawn from different days' production, for example. Processed products such as sausage or minced fish may be made with meat tissues from different days' or even different establishments' production. Although under some circumstances lots for sampling have been defined as products from the same consignor or packer, sample homogeneity can best be guaranteed when it is taken in conjunction with slaughter or primary collection point.

2. OBJECTIVES OF SAMPLING

2.1 Primary Point of Origin Sampling

2.1.1 Non-biased sampling

Non-biased sampling is designed to provide profile information on the occurrence of residues in specified food producing populations on an annual, national basis. For residue testing, the focus is on gathering information on the prevalence of residue violations; therefore, only compounds with established safe limits such as MRLVDs are usually considered for residue testing programmes. Compounds selected for statistically designed non-biased sampling are usually based on risk profiles (considering toxicity of residues and use) and the availability of laboratory methods suitable for regulatory control purposes. Information is obtained through a statistically based selection of random samples from animals presented for inspection. Limited or geographical area sampling may be conducted where a localized potential drug residue problem appears. The information obtained from this type of sampling should be reviewed periodically to assess residue control programmes and to allocate resources according to specific needs.

In addition to profile information, residue data provides a basis for further regulatory action. In particular, the results can be used to identify producers marketing animals, or other food commodity within the terms of reference of this Committee, with violative concentrations of residues. When these producers subsequently bring animals, fish or honey for inspection, they will be subjected to more directed and specific sampling and testing until compliance with MRLVDs is demonstrated. Other auxiliary uses of the data are to indicate prevalence and concentrations of residue violations, to evaluate residue trends, and to identify residue problem areas within the industry where educational or other corrective efforts may be needed. Thus, non-biased sampling gathers information and assists in deterring practices that lead to residue violations.

As a general practice, samples collected by inspectors are sent for residue analysis to a laboratory designated by national authorities. Now, however, advances in analytical technology provide inspection authorities an opportunity for performing residue screening tests on commodities at an abattoir or similar facility. In these situations, inspectors may send tissue samples to a laboratory designated by national authorities for more definitive analyses when results obtained from the screening test suggest a positive residue finding.

In some cases and situations where samples are sent directly to a designated laboratory for residue testing, the laboratory results may not be available until after the product has moved into consumer markets and become untraceable. Because of this pragmatic limitation, some animals, fish or honey containing violative residues may inevitably pass into consumer markets, regardless of the regulatory control efforts to limit this occurrence as much as possible. The consequences to human health, however, are minimal as long as the frequency of violative residues is low. This is because MRLVDs represent the maximum residue concentration determined to be safe for daily consumption within the limits of the acceptable daily intake (ADI) over a lifetime. As a result of employing safety

factors for determining an ADI, and subsequently the MRLVD, the occasional consumption of products with slightly higher residue concentrations than the MRLVD is unlikely to result in adverse health effects.

Non-biased sampling should have a statistically specified reliability. This may be expressed in reference to a confidence level and a prevalence rate. For example, sampling may be designed to detect, with 95% certainty, a prevalence occurring in 1% of healthy animals submitted for inspection. When a confidence level and prevalence rate is established, the number of samples necessary to achieve the desired objective can be determined from Table 1.

Table 1: Number of samples required to detect at least one violation with predefined probabilities (i.e., 90, 95, and 99 percent) in a population having a known violation prevalence.

Violation prevalence (% in a population)	Minimum number of samples required to detect a violation with a confidence level of:		
	90%	95%	99%
35	6	7	11
30	7	9	13
25	9	11	17
20	11	14	21
15	15	19	29
10	22	29	44
5	45	59	90
1	230	299	459
0.5	460	598	919
0.1	2302	2995	4603

2.1.2 Directed sampling

Directed sampling is designed to investigate and control the movement of potentially adulterated products. The sampling is often purposely biased and is directed at particular carcasses, products or producers in response to information from statistically based sampling (or other regulatory control agency data), or from inspector observations during ante-mortem or post-mortem inspection indicating that violative residues may be present. In-plant or on site residue testing procedures may be performed by the inspector, or samples may be submitted for analysis to a laboratory designated by national authorities. Depending upon the weight of evidence for testing in support of directed sampling, product may be retained until test results indicate the appropriate regulatory disposition. Laboratory analysis of directed residue test samples should be completed as rapidly as possible and take precedence over routine, statistically based samples. In directed sampling situations, herds of animals, flocks of birds, lots of fish or honey, should be considered unacceptable until it can be demonstrated that they are in compliance with Codex MRLVDs or national regulations in the country of origin for the specific commodity.

The probability of failing to detect a residue violation and accepting the lot depends upon the directed sampling programmes' sample size and prevalence of the residue violation frequency. Table 2 shows the probability of failing to detect a residue violation using different sample sizes from an "infinite" population with a specified proportion of violations. For example, selecting 5 samples from a large lot in which 10 percent of the units contain violative residues would, on the average, fail to detect a residue violation in 59.0 percent of such lots (i.e., 59.0 percent of the lots would be

accepted). Assuming the same conditions as the previous example, but using a sample size of 50, would result in only 0.5 percent of such lots being accepted.

Table 2: Probability of failing to detect a residue violation

Prevalence (%)	Number of animals in sample tested									
	5	10	25	50	75	100	200	250	500	1000
1	0.951	0.904	0.779	0.605	0.471	0.366	0.134	0.081	0.007	0.000
2	0.904	0.817	0.603	0.364	0.220	0.133	0.018	0.006	0.000	
3	0.859	0.737	0.467	0.218	0.102	0.048	0.002	0.000		
4	0.815	0.665	0.360	0.130	0.047	0.017	0.000			
5	0.774	0.599	0.277	0.077	0.021	0.006				
6	0.734	0.539	0.213	0.045	0.010	0.002				
7	0.696	0.484	0.163	0.027	0.004	0.001				
8	0.659	0.434	0.124	0.015	0.002	0.000				
9	0.624	0.389	0.095	0.009	0.001					
10	0.590	0.349	0.072	0.005	0.000					
12	0.528	0.279	0.041	0.002						
14	0.470	0.221	0.023	0.001						
16	0.418	0.175	0.013	0.000						
18	0.371	0.137	0.007							
20	0.328	0.107	0.004							
24	0.254	0.064	0.001							
28	0.193	0.037	0.000							
32	0.145	0.021								
36	0.107	0.012								
40	0.078	0.006								
50	0.031	0.001								
60	0.010	0.000								

Risk and cost factors should be considered in determining the sample sizes used in a directed sampling programme. Also, because of possible gains in the probability of detecting unacceptable herds of animals, flocks of birds, lots of fish or honey due to residue violations, the feasibility of selecting separate samples from separate lots instead of from a single lot should be considered.

2.2 Secondary Point of Sampling

2.2.1 Port of entry sampling

Port of entry testing of products derived from food producing animals, poultry, or fish, and honey, imported by member countries of Codex Alimentarius is a means of verifying the effectiveness of the exporting country's residue control programme. The purpose of port of entry sampling and testing is not to replace an exporting country's residue control programmes.

Results of residue testing that indicate imported product is in compliance with Codex MRLVDs should be permitted to move into commerce. When test results indicate that imported product contains violative residues, subsequent shipments of the same product group from that

establishment or company should be retained at the port of entry until laboratory results indicating compliance with MRLVDs are known by regulatory control authorities. Consideration should be given to placing all subsequent shipments of similar products from the country of origin on an increased testing schedule until a record of compliance with Codex MRLVDs is re-established.

Compounds selected for residue testing at port of entry should take into account the compounds approved for use in the exporting country, as well as those included in the domestic residue control programme of the importing and exporting country. Guidance for collecting samples for port of entry testing is summarized in Appendix A, Table A, Appendix B, Table B and Appendix C.

Appendix A

SAMPLING FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN MEAT AND POULTRY PRODUCTS

1. OBJECTIVE

To provide instructions for sampling a lot of meat or poultry products to determine compliance with Codex Maximum Residue Limits for Veterinary Drugs (MRLVDs).

2. DEFINITIONS

2.1 Lot

An identifiable quantity of food delivered for slaughter or distribution at one time, and determined to have common characteristics, such as origin, variety, type of packing, packer or consignor, or markings, by the sampling official. Several lots may make up a consignment.

2.2 Consignment

A quantity of food as described on a particular contractor's shipping document. Lots in a consignment may have different origins or may be delivered at different times.

2.3 Primary Sample

A quantity of tissue taken from a single animal or from one place in the lot, unless this quantity is inadequate for the residue analysis. When the quantity is inadequate, samples from more than one animal or location can be combined for the primary sample (such as poultry organs).

2.4 Bulk Sample

The combined total of all the primary samples taken from the same lot.

2.5 Final Sample

The primary sample or a representative portion of the primary sample to be used for control purposes.

2.6 Laboratory Sample

The sample intended for laboratory analysis. A whole primary sample may be used for analysis or the sample may be subdivided into representative portions, if required by national legislation.

3. COMMODITIES TO WHICH THE GUIDELINE APPLIES

3.1 Selected Class B: Primary Food Commodities of Animal Origin

Type 06 Mammalian Products

No. 030 Mammalian Meat

No. 031 Mammalian Fats

No. 032 Mammalian Edible Offal

Type 07 Poultry Products

No. 036 Poultry Meats

No. 037 Poultry Fats

No. 038 Poultry Edible Offal

3.2 Selected Class E: Processed Products of Animal Origin made from only Primary Food Nos. 030, 032, 036, and 038

Type 16 - Secondary Products

Type 18 - Manufactured (single ingredient) Products of a Minimum of One Kilogram Container or Unit Size

Type 19 - Manufactured (multiple ingredient) Products of a Minimum of One Kilogram Container or Unit Size

4. PRINCIPLE ADOPTED

For purposes of control, the maximum residue limit (MRLVD) is applied to the residue concentration found in each laboratory sample taken from a lot. Lot compliance with a Codex MRLVD is achieved when none of the laboratory samples contains a residue greater than the MRLVD.

5. EMPLOYMENT OF AUTHORIZED SAMPLING OFFICIALS

Samples must be collected by officials authorized for this purpose.

6. SAMPLING PROCEDURES

6.1 Product to Sample

Each lot to be examined must be sampled separately.

6.2 Precautions to Take

During collection and processing, contamination or other changes in the samples which would alter the residue or affect the analytical determination must be prevented.

6.3 Collection of a Primary Sample

Detailed instructions for collection of a primary sample of various products are provided in Table A. Quantities to collect are dependent on the analytical method requirements. Minimum quantity requirements are included in Table A. The following are general instructions.

- a. Each primary sample should be taken from a single animal or unit in a lot, and when possible, be selected randomly.
- b. When multiple animals are required for adequate sample size of the primary sample (i.e., poultry organs), the samples should be collected consecutively after random selection of the starting point.
- c. Canned or packaged product should not be opened for sampling unless the unit size is at least twice the amount required for the primary laboratory sample. The primary sample should contain a representative portion of juices surrounding the product. Each sample should then be frozen as described in paragraph 6.8.d.
- d. Frozen product should not be thawed before sampling.
- e. Large, bone-containing units of product (i.e., prime cuts) should be sampled by collecting edible product only as the primary sample.

6.4 The Number of Primary Samples to Collect from a Lot

The number of primary samples collected will vary depending on the status of the lot. If a residue violation is suspected because of its origin from a source with a past history of residue violations of the MRLVD, by evidence of contamination during transport, by signs of toxicosis observed during ante- or post-mortem inspection, or by other relevant information available to the inspection official, the lot is designated a suspect lot. If there is no reason to suspect adulteration, the lot is designated a non-suspect lot.

6.4.1 Sampling suspect lots

A minimum of six to a maximum of thirty primary samples should be collected from a suspect lot. When the suspected adulteration is expected to occur throughout the lot or is readily identifiable within the lot, the smaller number of samples is sufficient.

6.4.2 Sampling non-suspect lots

A statistically-based, non-biased sampling programme is recommended for non-suspect lots. Any of the following types of sampling can be used.

a. Stratified random sampling

In a complex system where commodities must be sampled at many locations over extended time periods, it is very difficult to apply simple random criteria in the design of a sampling programme. A useful alternative sampling design is stratified random sampling which separates population elements into non-overlapping groups, called strata. Then samples are selected within each stratum by a simple random design. Homogeneity within each stratum is better than in the whole population. Countries or geographic regions are natural strata because of uniformity in agricultural practices. Time strata (e.g., month, quarter) are commonly used for convenience, efficiency, and detection of seasonal variability. Random number tables or other objective techniques

should be used to ensure that all elements of a population have an equal and independent chance of being included in the sample.

b. Systematic sampling

Systematic sampling is a method of selecting a sample from every 'K' quantity of product to be sampled, and then sampling every 'K' unit thereafter. Systematic sampling is quicker, easier, and less costly than non-biased sampling, when there is reliable information on product volumes to determine the sampling interval that will provide the desired number of samples over time. If the sampling system is too predictable, it may be abused. It is advisable to build some randomness around the sampling point within the sampling interval.

c. Biased or estimated worst case sampling

In biased or estimated worst case sampling, the investigator should use their judgement and experience regarding the population, lot, or sampling frame to decide which samples to select. As a non-random technique, no inferences should be made about the population sampled based on data collected. The population group anticipated to be at greatest risk may be identified.

Exporting countries should conduct a comprehensive residue testing programme and provide results to importing countries. Based on an importing country's data, testing may be conducted as applied to non-suspect products. Countries that do not provide residue testing results showing compliance with MRLVDs should be sampled as suspect lots.

6.5 Preparation of the Bulk Sample

The bulk sample is prepared by combining and thoroughly mixing the primary samples.

6.6 Preparation of the Final Sample

The primary sample should, if possible, constitute the final sample. If the primary sample is too large, the final sample may be prepared from it by a suitable method of reduction.

6.7 Preparation of the Laboratory Sample

The final sample should be submitted to the laboratory for analysis. If the final sample is too large to be submitted to the laboratory, a representative subsample should be prepared. Some national legislation may require the final sample be subdivided into two or more portions for separate analysis. Each portion should be representative of the final sample. Precautions in paragraph 6.2 should be observed.

6.8 Packaging and Transmission of Samples

- a. Each sample should be placed in a clean, chemically inert container to protect the sample from contamination and from being damaged in shipping.
- b. The container should be sealed so that unauthorized opening is detectable.
- c. The container should be sent to the laboratory as soon as possible, after taking precautions against leakage and spoilage.
- d. For shipping, all perishable samples should be frozen to minus 20°C, immediately after collection, and packed in a suitable container that retards thawing. If possible,

the shipping container should be placed in a freezer for 24 hours prior to packing and shipping the frozen sample.

7. RECORDS

Each primary sample should be correctly identified by a record with the type of sample, its origin (e.g., country, state, or town), its location of collection, date of sampling, and additional information useful to the analyst or to regulatory officials for follow-up action if necessary.

8. DEPARTURE FROM RECOMMENDED SAMPLING PROCEDURES

If there is a departure from recommended sampling procedures, records accompanying the sample should fully describe procedures actually followed.

TABLE A: MEAT AND POULTRY PRODUCTS

	Commodity	Instructions for collection	Minimum quantity required for laboratory sample
I.	Group 030 (Mammalian Meats)		
A.	Whole carcass or side, unit weight normally 10 kg or more	Collect diaphragm muscle, supplement with cervical muscle, if necessary, from one animal.	500 g
B.	Small carcass (e.g., rabbit)	Collect hind quarter or whole carcass from one or more animals.	500 g after removal of skin and bone
C.	Fresh/chilled parts		
	1. Unit minimum weight of 0.5 kg, excluding bone (e.g., quarters, shoulders, roasts)	Collect muscle from one unit.	500 g
	2. Unit weighing less than 0.5 kg (e.g., chops, fillets)	Collect the number of units from selected container to meet laboratory sample size requirements.	500 g after removal of bone
D.	Bulk frozen parts	Collect a frozen cross-section from selected container, or take muscle from one large part.	500 g
E.	Retail packaged frozen/chilled parts, or individually wrapped units for wholesale	For large cuts, collect muscle from one unit or take sample from number of units to meet laboratory sample size requirements.	500 g after removal of bone
Ia.	Group 030 (Mammalian Meats where MRL is found in carcass fat)		
A.	Animals sampled at slaughter	See instructions under II. Group 031.	
B.	Other meat parts	Collect 500 g of visible fat, or sufficient product to yield 50-100 g of fat for analysis. (Normally 1.5-2.0 kg of product is required for cuts without trimmable fat).	Sufficient to yield 50-100 g of fat
II.	Group 031 (Mammalian Fats)		
A.	Large animals sampled at slaughter, usually weighing at least 10 kg	Collect kidney, abdominal, or subcutaneous fat from one animal.	500 g

	Commodity	Instructions for collection	Minimum quantity required for laboratory sample
B.	Small animals sampled at slaughter ²⁵	Collect abdominal and subcutaneous fat from one or more animals.	500 g
C.	Bulk fat tissue	Collect equal size portions from 3 locations in container.	500 g
III.	Group 032 (Mammalian Edible Offal)		
A.	Liver	Collect whole liver(s) or portion sufficient to meet laboratory sample size requirements.	400 - 500 g
B.	Kidney	Collect one or both kidneys, or kidneys from more than one animal, sufficient to meet laboratory sample size requirement. Do not collect from more than one animal if size meets the low range for sample size.	250 - 500 g
C.	Heart	Collect whole heart or ventricle portion sufficient to meet laboratory sample size requirement.	400 - 500 g
D.	Other fresh/chilled or frozen, edible offal product	Collect portion derived from one animal unless product from more than one animal is required to meet laboratory sample size requirement. A cross-section can be taken from bulk frozen product.	500 g
IV.	Group 036 (Poultry Meats)		
A.	Whole carcass of large bird, typically weighing 2-3 kg or more (e.g., turkey, mature chicken, goose, duck)	Collect thigh, leg, and other dark meat from one bird.	500 g after removal of skin and bone
B.	Whole carcass of bird typically weighing between 0.5-2.0 kg (e.g., young chicken, duckling, guinea fowl)	Collect thigh, legs, and other dark meat from 3-6 birds, depending on size.	500 g after removal of skin and bone
C.	Whole carcasses of very small birds typically weighing less than 500 g (e.g., quail, pigeon)	Collect at least 6 whole carcasses.	250 - 500 g of muscle tissue
D.	Fresh/chilled or frozen parts		
	1. Wholesale packaged		
	a. Large parts	Collect an interior unit from a selected container.	500 g after removal of skin and bone
	b. Small parts	Collect sufficient parts from a selected layer in the container.	
	2. Retail packaged	Collect a number of units from selected container to meet laboratory sample size requirement.	500 g after removal of skin and bone
IVa.	Group 036 (Poultry Meats where MRLVD is expressed in carcass fat)		
A.	Birds sampled at slaughter	See instructions under V. Group 037	
B.	Other poultry meat	Collect 500 g of fat or sufficient product to yield 50-100 g of fat. (Normally, 1.5-2.0 kg is required.)	500 g of fat or enough tissue to yield 50-100 g of fat
V.	Group 037 (Poultry Fats)		

²⁵ When adhering fat is insufficient to provide a suitable sample, the sole commodity without bone, is analyzed and the MRL will apply to the sole commodity.

	Commodity	Instructions for collection	Minimum quantity required for laboratory sample
A.	Birds sampled at slaughter	Collect abdominal fat from 3-6 birds, depending on size.	Sufficient to yield 50-100 g of fat
B.	Bulk fat tissue	Collect equal size portions from 3 locations in container.	500 g
VI.	Group 038 (Poultry Edible Offal)		
A.	Liver	Collect 6 whole livers or a sufficient number to meet laboratory sample requirement.	250 - 500 g
B.	Other fresh/chilled or frozen edible offal product	Collect appropriate parts from 6 birds. If bulk frozen, take a cross-section from container.	250 - 500 g
VII.	Class E - Type 16 (Secondary Meat and Poultry Products)		
A.	Fresh/chilled or frozen comminuted product of single species origin	Collect a representative fresh or frozen cross-section from selected container or packaged unit.	500 g
B.	Group 080 (Dried Meat Products)	Collect a number of packaged units in a selected container sufficient to meet laboratory sample size requirements.	500 g, unless fat content is less than 5% and MRLVD is expressed on a fat basis. Then 1.5-2.0 kg is required.
VIII.	Class E-Type 18 (Manufactured, single ingredient product of animal origin)		
A.	Canned product (e.g., ham, beef, chicken), unit size of 1 kg or more	Collect one can from a lot. When unit size is large (greater than 2 kg), a representative sample including juices may be taken.	500 g, unless fat content is less than 5% and MRLVD is expressed on a fat basis. Then 1.5-2.0 kg is required.
B.	Cured, smoked, or cooked product (e.g., bacon slab, ham, turkey, cooked beef), unit size of at least 1 kg	Collect portion from a large unit (greater than 2 kg), or take whole unit, depending on size.	500 g, unless fat content is less than 5% and MRLVD is expressed on a fat basis. Then 1.5-2.0 kg is required.
IX.	Class E - Type 19 (Manufactured, multiple ingredient, product of animal origin)		
A.	Sausage and luncheon meat rolls with a unit size of at least 1 kg	Collect cross-section portion from a large unit (greater than 2 kg), or whole unit, depending on size.	500 g

Appendix B

SAMPLING FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN FISH, MILK AND EGG PRODUCTS

1. OBJECTIVE

To provide instructions for sampling a lot of eggs, milk, or aquatic animal products, to determine compliance with Codex Maximum Residue Limits for Veterinary Drugs (MRLVDs).

2. DEFINITIONS

2.1 Lot

An identifiable quantity of food delivered for slaughter or distribution at one time, and determined to have common characteristics, such as origin, variety, type of packing, packer or consignor, or markings, by the sampling official. Several lots may make up a consignment.

2.2 Consignment

A quantity of food as described on a particular contractor's shipping document. Lots in a consignment may have different origins or be delivered at different times.

2.3 Primary Sample

A quantity of food taken from a single animal or from one place in the lot, unless this quantity is inadequate for the residue analysis. When the quantity is inadequate, samples from more than one location in the lot can be combined for the primary sample.

2.4 Bulk Sample

The combined total of all the primary samples taken from the same lot.

2.5 Final Sample

The bulk sample or a representative portion of the bulk sample to be used for control purposes.

2.6 Laboratory Sample

The sample intended for laboratory analysis. A whole primary sample may be used for analysis or the sample may be subdivided into representative portions, if required by national legislation.

3. COMMODITIES TO WHICH THE GUIDELINE APPLIES

3.1 Selected Class B: Primary Food Commodities of Animal Origin

Type 06 Mammalian Products

No. 033 Milks

Type 07 Poultry Products

No. 039 Eggs

Type 08 Aquatic Animal Products

No. 040 Freshwater Fish

No. 041 Diadromous Fish

No. 043 Fish Roe and Edible Offal of Fish

No. 045 Crustaceans

Type 09 Amphibians and Reptiles

No. 048 Frogs, Lizards, Snakes and Turtles

Type 10 Invertebrate Animals

No. 049 Molluscs and Other Invertebrate Animals

3.2 Selected Class E: Processed Products of Animal Origin made from only Primary Food Nos. 033, 039, 040, 041, 043, 045, 048, and 049

Type 16 - Secondary Products

Type 17 - Derived Edible Products of Aquatic Animal Origin

Type 18 - Manufactured (single ingredient) Products of a Minimum of One Kilogram Container or Unit Size

Type 19 - Manufactured (multiple ingredient) Products of a Minimum of One Kilogram Container or Unit Size

4. PRINCIPLE ADOPTED

For purposes of control, the maximum residue limit (MRLVD) is applied to the residue concentration found in each laboratory sample taken from a lot. Lot compliance with a Codex MRLVD is achieved when none of the laboratory samples contains a residue greater than the MRLVD.

5. EMPLOYMENT OF AUTHORIZED SAMPLING OFFICIALS

Samples must be collected by officials authorized for this purpose.

6. SAMPLING PROCEDURES

6.1 Product to Sample

Each lot to be examined must be sampled separately.

6.2 Precautions to Take

During collection and processing, contamination or other changes in the samples must be prevented which would alter the residue, affect the analytical determination, or make the laboratory sample not representative of the bulk or final sample.

6.3 Collection of a Primary Sample

Detailed instructions for collection of a primary sample of various products are provided in Table B. Quantities to collect are dependent on the analytical method requirements. Minimum quantity requirements are included in Table B. The following are general instructions.

- a. Each primary sample should be taken from a single unit in a lot, and when possible, be selected randomly.
- b. Canned or packaged product should not be opened for sampling unless the unit size is at least twice the amount required for the primary laboratory sample. Each primary sample should contain a representative portion of juices surrounding the product. Each sample should then be frozen as described in paragraph 6.8.d.
- c. Frozen product should not be thawed before sampling.

6.4 The Number of Primary Samples to Collect from a Lot

The number of primary samples collected will vary depending on the status of the lot. If a residue violation is suspected because of its origin from a source with a past history of residue violations of the MRLVD, by evidence of contamination during transport or by other relevant information to the inspection official, the lot is designated a suspect lot. If there is no reason to suspect adulteration, the lot is designated a non-suspect lot.

6.4.1 Sampling suspect lots

A minimum of six to a maximum of thirty primary samples should be collected from a suspect lot. When the suspected adulteration is expected to occur throughout the lot or is readily identifiable within the lot, the smaller number of samples is sufficient.

6.4.2 Sampling non-suspect lots

A statistically-based, random sampling programme is recommended for non-suspect lots. Any of the following types of sampling can be used.

a. Stratified random sampling

In a complex system where commodities must be sampled at many locations over extended time periods, it is very difficult to apply simple random criteria in the design of a sampling programme. A useful alternative sampling design is stratified random sampling which separates population elements into non-overlapping groups, called strata. Then samples are selected within each stratum by a simple random design. Homogeneity within each stratum is better than in the whole population. Countries or geographic regions are natural strata because of uniformity in agricultural practices. Time strata (e.g., month, quarter) are commonly used for convenience, efficiency, and detection of seasonal variability. Random number tables or other objective techniques should be used to ensure that all elements of a population have an equal and independent chance of being included in the sample.

b. Systematic sampling

Systematic sampling is a method of selecting a sample from every 'K' quantity of product to be sampled, and then sampling every 'K' unit thereafter. Systematic sampling is quicker, easier, and less costly than random sampling, when there is reliable information on product volumes to be used to determine the sampling interval that will provide the desired number of samples over time. If the sampling system is too predictable, it may be abused. It is advisable to build some randomness around the sampling point within the sampling interval.

c. Biased or estimated worst case sampling

In biased or estimated worst case sampling, the investigator should use their own judgement and experience regarding the population, lot, or sampling frame to decide which samples to select. As a non-random technique, no inferences should be made about the population sampled based on data collected. The population group anticipated to be at greatest risk may be identified.

Exporting countries should conduct a comprehensive residue testing programme and provide results to importing countries. Based on an importing country's data, testing may be conducted as applied to non-suspect products. Countries which do not provide residue testing results showing compliance with MRLVDs should be sampled as suspect lots.

6.5 Preparation of the Bulk Sample

The bulk sample is prepared by combining and thoroughly mixing the primary samples.

6.6 Preparation of the Final Sample

The primary sample should, if possible, constitute the final sample. If the primary sample is too large, the final sample may be prepared from the primary sample by a suitable method of reduction.

6.7 Preparation of the Laboratory Sample

The final sample should be submitted to the laboratory for analysis. If the final sample is too large to be submitted to the laboratory, a representative subsample should be prepared. Some national legislation may require the final sample be subdivided into two or more portions for separate analysis. Each portion should be representative of the final sample. Precautions in paragraph 6.2 should be observed.

6.8 Packaging and Transmission of Samples

- a. Each sample or subsample should be placed in a clean, chemically inert container to protect the sample from contamination and from being damaged in shipping.
- b. The container should be sealed so that unauthorized opening is detectable.
- c. The container should be sent to the laboratory as soon as possible, after taking precautions against leakage and spoilage.
- d. For shipping, all perishable samples should be frozen to minus 20°C, immediately after collection, and packed in a suitable container that retards thawing. If possible,

the shipping container should be placed in a freezer for 24 hours prior to packing and shipping the frozen sample.

7. RECORDS

Each sample must be correctly identified by a record with the type of sample, origin of the sample (e.g., country, state, or town), location of collection of the sample, date of sampling, and additional information useful to the analyst or to regulatory officials for follow-up action if necessary.

8. DEPARTURE FROM RECOMMENDED SAMPLING PROCEDURES

If there is a departure from recommended sampling procedures, records accompanying the sample should fully describe procedures actually followed.

TABLE B: MILK, EGGS, DAIRY PRODUCTS AND AQUATIC ANIMAL PRODUCTS

Commodity		Instructions for collection	Minimum quantity required for laboratory sample
I.	Group 033 (Milks)		
	Whole liquid milk raw, pasteurized, UHT & sterilized	In bulk. Mix thoroughly and immediately take a sample by means of a dipper. In retail containers. Take sufficient units to meet laboratory sample size requirements.	500 ml
II.	Group 082 (Secondary Milk Products)		
A.	Skimmed milk skimmed and semi-skimmed	As for whole liquid milk.	500 ml
B.	Evaporated milk evaporated full cream & skimmed milk	Bulk containers (barrels, drums). Mix the contents carefully and scrape adhering material from the sides and bottom of the container. Remove 2 to 3 litres, repeat the stirring and take a 500 ml sample. Small retail containers. Take sufficient units to meet laboratory sample size requirements.	500 ml
C.	Milk powders		
	1. Whole	Bulk containers. Pass a dry borer tube steadily through the powder at an even rate of penetration. Remove sufficient bores to make up a sample of 500 g. Small retail containers. Take sufficient units to meet laboratory sample size requirements.	500 g
	2. Low fat	As for whole milk powders.	500 g

Commodity		Instructions for collection	Minimum quantity required for laboratory sample
III. Group 087 (Derived Milk Products)			
A.	Cream fresh, frozen & UHT; single, whipping, whipped, double & clotted	Bulk containers. Plunge to ensure thorough mixing moving the plunger from place to place avoiding foaming, whipping and churning. Take a 200 ml sample by means of a dipper.	200 ml
		Small containers. Take sufficient units to meet laboratory sample size requirements.	
B.	Butter including whey butter and low fat spreads containing butterfat	In bulk. Take two cores or more of butter so that the minimum total sample weight is not less than 200 g	200 g
		In pats or rolls. For units weighing over 250 g divide into four and take opposite quarters. For units weighing less than 250 g take one unit as sample.	
C.	Butteroil including anhydrous butteroil and an- hydrous milkfat	Mix thoroughly and take a 200 g sample.	200 g
IV. Group 090 (Manufactured Milk Products - single ingredient)			
A.	Yoghurt natural, low fat through to full cream	Select number of units sufficient to meet laboratory requirements.	500 g
B.	Cheeses all varieties	Make two cuts radiating from the centre of the cheese if the cheese has a circular base, or parallel to the sides if the base is rectangular. The piece removed should meet the laboratory sample size requirements. For small cheeses and wrapped portions of cheese take sufficient units to meet laboratory sample requirements.	200 g
V. Group 092 (Manufactured Milk Products - multi- ingredient)			
A.	Dairy ice cream only ice cream containing 5% or greater of milk fat	Select block or units sufficient to meet laboratory sample size requirements.	500 ml
B.	Processed cheese preparations	Select units sufficient to meet laboratory sample size requirements.	200 g
C.	Flavoured yoghurt	As for natural yoghurt.	500 g
D.	Sweetened condensed milk	As for evaporated milk.	500 ml
VI. Group 039 (Eggs and Egg Products)			
A.	Liquid and frozen eggs	Use sample schedule. Subsample size will be 0.25 litre liquid or 0.5 litre packed shavings from aseptic drillings into containers.	500 g

Commodity		Instructions for collection	Minimum quantity required for laboratory sample
B.	Dried egg products	Use sample schedule. For containers of 0.5 kg or less or 0.25 litre or less, collect a minimum of 2 units per subsample. For containers of 0.5 to 10 kg select 1 unit per subsample. for containers of 10 kg or more collect 1 kg from each unit sampled. Collect with aseptic technique.	500 g
C.	Shell eggs		
	1. Retail packages	Use sample schedule. Subsample size is 1 dozen.	500 g or 10 whole eggs
	2. Commercial cases	For 15 cases or less collect 1 dozen from each case, minimum of 2 dozen eggs. For 16 or more cases collect 1 dozen from 15 random cases.	500 g or 10 whole eggs
VII. Class B - Type 08 (Aquatic Animal Products)			
A.	Packaged fish fresh, frozen, smoked, cured, or shellfish (except oysters)	Collect 12 subsamples randomly. Minimum subsample size is 1 kg.	1000 g
B.	Bulk fish 0.5 - 1.5 kg	Collect 12 subsamples randomly. Each subsample should total 0.5 kg of edible fish.	1000 g
C.	Bulk shellfish (except oysters)	Collect 12 subsamples randomly.	1000 g
D.	Other fish and shellfish products (including oysters)	Collect 12 - 0.25 litre subsamples.	1000 g
VIII. Class E - Type 17 (Derived Edible Products of Aquatic Animal Origin)			
A.	Canned fish and shellfish products (except oysters)	Collect 12 subsamples of 5 cans per subsample.	1000 g
B.	Other fish and shellfish products - fish flour and meal	Use sample schedule. Collect 1 kg per subsample.	1000 g

Appendix C

SAMPLING FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN HONEY

1. OBJECTIVE

To provide instructions for sampling a lot of honey to determine compliance with Codex Maximum Residue Limits for Residues of Veterinary Drugs (MRLVDs).

2. DEFINITIONS

2.1 Lot

An identifiable quantity of food (honey) delivered for distribution at one time, and determined to have common characteristics, such as origin, variety, type of packing, packer or consignor, or markings, by the sampling official. Several lots may make up a consignment.

2.2 Consignment

A quantity of food (honey) as described on a particular contractor's shipping document. Lots in a consignment may have different origins or may be delivered at different times.

2.3 Primary Sample

A quantity of honey taken from one place in the lot, unless this quantity is inadequate for the residue analysis. When the quantity is inadequate, samples from more than one location can be combined for the primary sample.

2.4 Bulk Sample

The combined total of all the primary samples taken from the same lot.

2.5 Final Sample

The bulk sample or a representative portion of the bulk sample to be used for control purposes.

2.6 Laboratory Sample

The sample intended for laboratory analysis. A whole primary sample may be used for analysis or the sample may be subdivided into representative portions, if required by national legislation.

3. COMMODITIES TO WHICH THE GUIDELINE APPLIES

3.1 Selected According to Origin

Blossom or nectar honey that comes mainly from nectaries of flowers.

Honeydew honey that comes mainly from secretions of or on living parts of plants.

3.2 Selected According to Mode of Processing

Comb honey that is stored by bees in the cells of freshly built broodless combs, and sold in sealed whole combs or sections of such combs.

Extracted honey that is obtained by centrifuging decapped broodless combs.

Pressed honey that is obtained by pressing broodless combs with or without the application of moderate heat.

4. PRINCIPLE ADOPTED

For purposes of control, the maximum residue limit (MRLVD) is applied to the residue concentration found in each laboratory sample taken from a lot. Lot compliance with a Codex MRLVD is achieved when none of the laboratory samples contain a residue greater than the MRLVD.

5. EMPLOYMENT OF AUTHORIZED SAMPLING OFFICIALS

Samples must be collected by officials authorized for this purpose.

6. SAMPLING PROCEDURES

6.1 Product to Sample

Each lot to be examined must be sampled separately.

6.2 Precautions to Take

During collection and processing, contamination or other changes in the samples must be prevented which would alter the residue, affect the analytical determination, or make the laboratory sample not representative of the bulk or final sample.

6.3 Collection of a Primary Sample

Quantities to collect are dependent on the analytical method requirements. Minimum quantity requirements and detailed instructions for collection of a primary sample of honey are provided in Appendix C, paragraph 9. The following are general instructions.

- a. Each primary sample should be taken from a single unit in a lot, and when possible, be selected randomly.
- b. Packaged product should not be opened for sampling unless the unit size is at least twice the amount required for the primary laboratory sample. The primary sample should contain a representative portion of the product. Each sample should be prepared for analysis as referenced in paragraph 6.5.

6.4 The Number of Primary Samples to Collect from a Lot

The number of primary samples collected will vary depending on the status of the lot. If adulteration is suspected by origin from a source with a past history of residue violations of the MRLVD, by evidence of contamination during transport or by the availability of other relevant information to the inspection official, the lot is designated a suspect lot. If there is no reason to suspect adulteration, the lot is designated a non-suspect lot.

6.5 Preparation of the Primary Sample

The primary sample is prepared as described in paragraph 9.

6.6 Preparation of the Laboratory Sample

The primary sample should, if possible, constitute the final sample. If the primary sample is too large, the final sample may be prepared from it by a suitable method of reduction.

6.7 Preparation of the Laboratory Sample

The final sample should be submitted to the laboratory for analysis. If the final sample is too large to be submitted to the laboratory, a representative subsample should be prepared. Some national legislation may require that the final sample be subdivided into two or more portions for separate analysis. Each portion should be representative of the final sample. Precautions in paragraph 6.2 should be observed.

6.8 Packaging and Transmission of Primary Samples

- a. Each primary sample should be placed in a clean, chemically inert container to protect the sample from contamination and from being damaged in shipping.
- b. The container should be sealed so that unauthorized opening is detectable.
- c. The container should be sent to the laboratory as soon as possible, after taking precautions against leakage and spoilage.

7. RECORDS

Each primary sample should be correctly identified by a record with the type of sample, its origin (e.g., country, state, or town), its location of collection, date of sampling, and additional information useful to the analyst or to regulatory officials for follow-up action if necessary.

8. DEPARTURE FROM RECOMMENDED SAMPLING PROCEDURES

If there is a departure from recommended sampling procedures, records accompanying the sample should fully describe procedures actually followed.

9. SAMPLING INSTRUCTIONS

9.1 Liquid or Strained Honey

If sample is free from granulation, mix thoroughly by stirring or shaking; if granulated, place closed container in water-bath without submerging, and heat 30 min at 60°C; then if necessary heat at 65°C until liquefied. Occasional shaking is essential. Mix thoroughly and cool rapidly as soon as sample liquefies. If foreign matter, such as wax, sticks, bees, particles of comb, etc., is present, heat sample to 40°C in water-bath and strain through cheesecloth in hot-water-funnel before sampling.

Collect 250 ml of liquid or strained honey.

9.2 Comb Honey

Cut across top of comb, if sealed, and separate completely from comb by straining through a sieve the meshes of which are made by so weaving wire as to form square opening of 0.500 mm by 0.500 mm (ISO 565-1983)²⁶. When portions of comb or wax pass through sieve, heat samples as in paragraph 9.1 and strain through cheesecloth. If honey is granulated in comb, heat until wax is liquefied; stir, cool and remove wax.

Collect 250 ml of liquid honey.

²⁶ Such sieve could be replaced by US sieve with No. 40 standard screen (size of opening 0.420 mm).

PART II

GENERAL CONSIDERATIONS ON ANALYTICAL METHODS FOR RESIDUE CONTROL

It would be ideal to have analytical methods available for determining compliance with MRLVDs that are effective and practical to detect, quantify, and identify all residues of veterinary drugs and pesticides (used as veterinary drugs) that may be present in commodities within the terms of reference of this Codex Committee. These methods could be routinely used by regulatory control authorities of member governments for their residue testing programmes to assure compliance with food safety requirements.

Methods with the capabilities mentioned above are not available for many compounds of interest because of the extensive number of potential veterinary drug residues which may find their way into food within the terms of reference of the CCRVDF. To optimize the effectiveness of regulatory programmes to test for veterinary drug residues, residue control programmes must use available residue methodology to assure compliance with Codex MRLVDs and, as necessary, take appropriate regulatory action against adulterated products, consistent with the reliability of the analytical data.

To assist regulatory authorities in determining their analytical needs for residue control programmes, this document will describe the types of methods available and a set of attributes which residue control programmes may utilize in carrying out their missions.

The principal attributes of analytical methods for residue control programmes are specificity, precision, accuracy (measured as systematic error and recovery), and sensitivity. Determining these principal attributes in a method requires well designed multi-laboratory studies. The attributes noted above will be presented in a subsequent section of this paper in more detail.

TYPES OF ANALYTICAL METHODS

Several types of methods are available to food safety agencies and programmes to conduct analyses that are consistent with the needs of residue testing programmes. Decisions on the use of a specific analytical method depends on the intended objectives of the regulatory programme and the analytical performance characteristics of methods.

Methods that are suitable for determining compliance with MRLVDs are those that have successfully completed an extensive multi-laboratory study for specific tissue and species combinations. These methods provide analytical results for either quantitation or identification that are appropriate to take regulatory action without the need for additional analyses. In some cases, these methods may be considered reference methods, but reference methods frequently are not routine.

Many methods currently being used by residue control programmes have successfully completed a multi-laboratory study. Multi-laboratory method performance studies generally satisfy these analytical requirements. Validated methods are those subjected to a properly designed inter-laboratory study with three or more analysts, and preferably, in three different laboratories. Collaborative study methods have successfully completed method evaluation in six or more laboratories in an acceptable, statistically designed study. Some residue control methods that have demonstrated their usefulness for determining compliance with MRLVDs have an historical origin. These history based methods were considered to be the best available at the time of initial regulatory

use and have continued in use over an extended period of time in the absence of more effective validated methods.

Collaborative study and validated methods may be extended to additional tissues, species, products, or combinations of these, not included in the original multi-laboratory study by completing additional properly designed laboratory studies. On a case by case basis, analytical results from method extension studies may require additional analysis and/or review before reporting results or taking regulatory action.

Methods that have not been validated by traditional inter-laboratory study, but provide results that may be correlated and compared with data obtained from a collaborative study or validated method, may serve a regulatory purpose. The validated and non-validated methods must be compared in a statistically acceptable study design using portions of the same (homogeneous) samples prepared for this comparison. The data from these studies should be reviewed by a peer group of regulatory scientists to determine the comparability of method performance.

There are some non-routine veterinary drug residue methods suitable for enforcement of MRLVDs. These methods may not have been subjected to an inter-laboratory study because they require specialized expertise or equipment. Good quality control and quality assurance procedures must be applied with these methods. Analytical data obtained from these methods should be reviewed by a peer group of regulatory analysts before recommending any regulatory action. These analytical methods may require analysis by another method to corroborate the initial experimental findings.

Occasionally, a method may be suitable for Codex purposes because the toxicology of an analyte does not allow an MRLVD to be established. Methods for analytes such as chloramphenicol would be in this category. Some methods in this category will include those presented above which are not sufficiently sensitive to quantitate and/or identify analyte(s) at or below the MRLVD. Such methods also may not meet other performance factors stated above.

There are some methods for which additional analysis is required to support regulatory action. This category may include methods that do not provide adequate information of structure or residue concentration. Analytical methods that may have been subjected to ruggedness testing, but not successfully to a multi-laboratory study to evaluate method performance, may have limited usefulness in a residue control programme. However, these methods may be useful in non-recurring or infrequent residue analyses, but they commonly require use of a rigorous protocol for sample analysis. Results from such methods should be considered only as estimates of analyte concentration or identification without additional supporting analytical information. Results from these methods can be useful for gathering residue information and determining whether there is a need to develop a more definitive method. These methods should not be used alone for residue control purposes on official samples without additional information (e.g., such as the presence of an injection site in the sample).

Certain methods may only be suitable for determining whether or not a veterinary drug residue problem exists in a sampling population. Methods in this category are used for information gathering, or exploratory residue control studies. Exploratory studies may also be undertaken using methods which have not been subjected to inter-laboratory study. These non-routine methods may be complex, or require highly specialized instrumentation, and may have been developed and used only in a single laboratory. Analytical results from these methods should not be used independently for taking regulatory action, but may be used to determine the need for additional testing and/or development of a method suitable for routine enforcement of MRLVDs.

Methods designed to analyze large numbers of samples quickly may be useful for determining the presence or absence of one or more compounds in a quantitative or semi-quantitative manner, at or above a specified concentration. Results at or above the MRLVD commonly require additional

analysis using a method with acceptable performance characteristics before taking regulatory action. Results from methods of this type that are below the MRLVD but above a level of reliable measurement of a more definitive method, may have limited use in determining exposure patterns.

METHOD DEVELOPMENT CONSIDERATIONS

Developing an analytical method requires analysts, laboratory space, equipment, and financial support. To optimize the benefit of these resources, it is important to provide introductory and background information to establish a perspective for planning an analytical method development project, and for evaluating the performance of the analytical method.

Residue control programmes should use methodology suitable to the analytes of interest to assure a safe and wholesome food supply. Necessary and appropriate regulatory action should be taken against adulterated products, consistent with the reliability of the analytical data. Before initiating method development activities, the intended use and need for a method in a residue control programme should be established. Other considerations include the compound or class of compounds of interest (and potential interfering substances), potential measurement systems and their properties, the pertinent physical and chemical properties that may influence method performance, the specificity of the desired testing system and how it was determined, analyte and reagent stability data and purity of reagents, the acceptable operating conditions for meeting method performance factors, sample preparation guidelines, environmental factors that may influence method performance, safety items, and any other specific information pertinent to programme needs.

ANALYTICAL PERFORMANCE CHARACTERISTICS

Specificity is the ability of a method to distinguish between the analyte of interest and other substances which may be present in the test sample. A residue control method must be able to provide unambiguous identification of the compound being measured. The ability to quantitatively differentiate the analyte from homologues, analogues, or metabolic products under the experimental conditions employed is an important consideration of specificity.

Precision of a method is the closeness of agreement between independent test results obtained from homogeneous test material under the stipulated conditions of use. Analytical variability between different laboratories is defined as reproducibility, and variability from repeated analyses within a laboratory is repeatability. Precision of a method is usually expressed as standard deviation. Another useful term is relative standard deviation, or coefficient of variation (the standard deviation, divided by the absolute value of the arithmetic mean). It may be reported as a percentage by multiplying by one hundred. Method variability achieved in the developing laboratory after considerable experience with a method, is usually less than the variability achieved by other laboratories that may later also use the method. For this reason, analytical data from a method should be statistically analyzed by procedures described by Youden and Steiner (Ref: Statistical Manual of the AOAC, AOAC INTERNATIONAL, Gaithersburg, MD, 1975) before preparing a final method write up. If a method cannot achieve a suitable level of performance in the developing laboratory, it cannot be expected to do any better in other laboratories.

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. Accuracy is closely related to systematic error (analytical method bias) and analyte recovery (measured as percent recovery). The accuracy requirements of methods will vary depending upon the planned regulatory use of the results. Generally, the accuracy at and below the MRLVD or level of interest must be equal to or greater than the accuracy above the level of interest.

The percent recovery of analyte added to a blank test sample is a related measurement that compares the amount found by analysis with 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 residue). At relatively high concentrations, analytical recoveries are expected to approach one hundred percent. At lower concentrations and, particularly with methods involving a number of steps including extraction, isolation, purification, and concentration, recoveries may be lower. Regardless of what average recoveries are observed, recovery with low variability is desirable.

The sensitivity of a method is a measure of its ability to detect the presence of an analyte and to discriminate between small differences in analyte concentration. Sensitivity also requires the ability to differentiate between analyte, related compounds and background interferences. For analytical instruments used in residue analysis, sensitivity is determined by two factors: instrumental response to the analyte and background interference, or instrument noise. Response is measured by the slope of the calibration curve with analyte standards at concentrations of interest. An ideal situation would be afforded by a linear curve. Instrument noise is the response produced by an instrument when no analyte is present in the test sample.

There are a number of collateral attributes suitable for analytical methods for regulatory control programmes beyond these principle method attributes. Methods should be rugged or robust, cost effective, relatively uncomplicated, portable, and capable of simultaneously handling a set of samples in a time effective manner. Ruggedness of a method refers to results being relatively unaffected by small deviations from the optimal amounts of reagents used in the analytical method, time factors for extractions or reactions, or temperature. This does not provide latitude for carelessness or haphazard techniques. Cost-effectiveness is the use of relatively common reagents, instruments, or equipment customarily available and used in a laboratory devoted to veterinary drug residue analyses. An uncomplicated method uses simple, straightforward mechanical or operational procedures throughout the method.

Portability is the analytical method characteristic that enables it to be transferred from one location to another without loss of established analytical performance characteristics.

The capability of a residue control method to simultaneously analyze a set of samples aids in method efficiency by allowing sets or batches of samples to be analyzed at the same time. This attribute reduces the analytical time requirements of sample analysis. It provides, for example, the capability of completing four or more analyses in a normal working day. This is important when large numbers of samples must be analyzed in short or fixed time frames.

Establishing method performance attributes is very important. These attributes provide the necessary information for food safety agencies to develop and manage their public health programmes. Performance attributes for analytical methods also provide a basis for good management decisions in future planning, evaluation, and product disposition. For the animal health care industry, it provides a guideline for knowing exactly what performance must be achieved in developing analytical procedures. All will benefit by having well defined analytical method performance factors.

INTEGRATING ANALYTICAL METHODS FOR RESIDUE CONTROL

Residue control and standard setting organizations have different terminologies to describe application of analytical methods. Methods of analysis for veterinary drug residues in foods must ultimately be able to reliably detect the presence of an analyte of interest, determine its concentration, and correctly identify the analyte at and above an established maximum residue limit (MRLVD) for regulatory enforcement actions to be taken. The latter methods would be classified as confirmatory

methods. These confirmatory methods may or may not have a quantitative or semi-quantitative component.

Other types of methods that may be used in residue control programmes, and which can strengthen such a programme, may be classified into two additional categories. These categories are quantitative methods and screening methods. Quantitative methods provide precise information concerning the amount of an analyte that may be present, but may only provide indirect information about the structural identity of the analyte. Screening methods may quickly determine the presence of one or more compounds, based upon one or more common characteristic of a class of veterinary drugs in a qualitative or semi-quantitative manner at a specified concentration limit. They may also determine that an analyte is below the limit of detection of the screening method.

These three categories of methods, confirmatory, quantitative, and screening, often share a common set of performance characteristics described above. In addition, they may have other specific considerations. Understanding the relationship between these three categories of methods is important in the development and operation of a balanced residue control programme. Screening methods are useful because they provide greater analytical efficiency (i.e., a greater number of analyses may be performed in a given time frame) than quantitative and/or confirmatory methods. In many circumstances screening methods can be performed in non-laboratory environments. Screening methods suitable for use in non-laboratory environments may be less expensive for regulatory control programmes than conducting all testing within a laboratory setting. Screening methods can be to separate test samples with no detectable residue from those that indicate the presence of a veterinary drug residue at or below an MRLVD or an appropriate level of interest. This would allow a laboratory to focus more of its efforts on quantitation of the presumptive positive test samples of regulatory interest.

Screening tests may also be used efficiently in a laboratory setting because they analyze a larger numbers of samples in a given time frame than their corresponding quantitative methods. The cost savings may not be as great as when screening methods are used in non-laboratory environments because the costs associated with the handling and shipping of samples must still be incurred. Presumptive positive results obtained from laboratory screening methods should not be used independently in taking regulatory action. Data obtained from such methods may be used to determine the need for additional testing and/or the development of a method suitable for routine enforcement of MRLVDs.

METHOD DEVELOPMENT AND VALIDATION CONSIDERATIONS FOR RESIDUE CONTROL METHODS

The multi-laboratory method validation study is the most important factor in providing analytical data to define method performance characteristics.

In developing a residue control method, whenever possible, data should be collected from three types of samples. Control test material from non-treated animals provides information about analytical background and matrix interferences. Fortified test material, containing known amounts of the analyte added to the control material, yields information about the method's ability to recover the analyte of interest under controlled conditions. Dosed or biologically incurred tissue, from food producing animals and birds that have been treated with the drug, provide additional analytical performance information about biological or other interactions that may occur when analyzing residue control samples.

Residue methods should be designed with as much simplicity as possible. Analytical simplicity helps minimize the variety, size, and type of glassware and equipment needed, minimizes the potential for analytical errors, and reduces laboratory and method costs. Reagents and standards

must be available commercially or from some other reliable source. Instrumentation should be selected based on its performance characteristics rather than a particular manufacturer.

Residue methods are sometimes designed using internal standards for analytical control. A properly used internal standard will compensate for some of the analytical variability of an analysis, improving precision. However, an improperly used internal standard may obscure variables that are an important part of the analytical measurement. If an internal standard is used, it should be added to a sample as early as possible in the procedure, preferably to the test material before analysis begins. Caution must be taken in the choice of internal standards to ensure that they do not alter the percent recovery of the analyte of interest or interfere with the measurement process. It is important to know the extent and predictability of the effects of the internal standard on an analytical method. Internal standards can greatly enhance method performance when used properly.

Residue control methods that may be subjected to widely variable physical test environments will place some additional requirements on methods. Addressing these may help improve method ruggedness. Warmer environments may require reagents to be more thermally stable, while solvents used in the analysis will have to be less volatile, and test sample requirements to be more lenient. Cooler environments may require reagents and solvents to have different physical properties, such as lower freezing point and greater solvating characteristics, to ensure effective extraction of an analyte. Environmental temperatures may influence the time required to perform an analysis, as well as influencing reaction rates, gravitational separations and colour development. These considerations may strain efforts to standardize methods for use in broadly differing environments because of the need to adapt methods to compensate for these factors.

An analytical method developed and used in only one laboratory may have limited use in a residue control programme. The reliability of reported values may be a concern even though strong quality control procedures may have been employed. As a minimum, three laboratories expected to use these methods should be used to develop performance characteristics for residue control, including analytical variability, and obtain statistically acceptable agreement on the same samples divided among the testing laboratories. Methods with higher reliability for residue testing should be able to successfully undergo a collaborative study involving at least six different laboratories (Ref: *Use of Statistics to Develop and Evaluate Analytical Methods* (by G.T. Wernimont and W. Spendley, AOAC INTERNATIONAL, Gaithersburg, MD), and *Compound Evaluation and Analytical Capability National Residue Programme Plan 1990*, (section 5, USDA, Food Safety and Inspection Service, Washington, D.C.)).

The principles for conducting either a validation or collaborative study of a residue control method are the same. Samples for evaluating method performance should be unknown to the analyst, contain the residue near the MRLVD as well as samples with the analyte above and below the level of interest, and test material blanks. All study samples should be analyzed over a limited number of days, preferably with replicate analysis, to improve statistical evaluation of method performance. It should be noted that these are only minimal requirements. Duplicate analyses in only six laboratories with one or two animal species and tissues would yield limited quality estimates for repeatability and reproducibility.

Quality control and quality assurance principles are essential components of residue analysis. They provide the basis for ensuring optimum method performance for all methods, regardless of method attributes, whenever they are used. Quality control monitors those factors associated with the analysis of a sample by a tester, while quality assurance provides the oversight by independent reviewers to ensure that the analytical programme is performing in an acceptable manner. Quality control and quality assurance programmes are invaluable to support decision-making for residue control agencies, improving the reliability of analytical results, and providing quality data for residue

control programmes to demonstrate food safety to consumers, producers, and law making bodies regarding residues of veterinary drugs in food.

PART III

ATTRIBUTES OF ANALYTICAL METHODS FOR RESIDUES OF VETERINARY DRUGS IN FOODS

The performance characteristics of analytical methods for determining compliance with MRLVDs must be defined and proposed methods evaluated accordingly. This will ensure reliable analytical results and provide a secure basis for determining residues of veterinary drugs in foods for commodities in international trade. Part II, *General Considerations of Analytical Methods for Regulatory Control*, presents a discussion of general types or categories of regulatory methods, and provides a scheme for using these analytical methods based upon their intended purpose in a regulatory framework. In the discussion below, attributes common to three categories of methods for determining compliance with Codex MRLVDs referred to as Level I, Level II and Level III methods will be presented followed by additional attributes that are applicable to only one or two categories of methods.

(Note: This Part contains numerous definitions. The CCRVDF has attempted to harmonize these definitions with those provided in the "Definitions for the Purpose of the Codex Alimentarius" in Volume 1.)

GENERAL CRITERIA FOR ATTRIBUTES

All methods may be characterized by a set of attributes or properties that determine their usefulness: *specificity* - what is being measured; *precision* - the variability of the measurement; and *systematic error* or *bias* - measured as analytical recovery. Another attribute, *accuracy*, usually refers to the closeness of agreement, or trueness of an analytical result, between the true value and the mean value obtained by analyzing a large number of samples of the test material. For semi-quantitative methods and screening methods, accuracy may also be defined as a measure of false negative and false positive responses. The *limit of detection*, *method sensitivity*, *practicality of use*, *tissue/species applicability*, *limit of detection* and *limit of quantitation* are additional attributes that have varying relevance to some methods, depending upon the intended use of the analytical results.

Methods may be described according to performance attributes as an alternative to classifying them by intent of use or purpose. This alternative approach defines methods by the analytical information and detail provided concerning the amount and nature of the analyte(s) of interest. Level I methods are the most definitive, while Level III methods usually provide general information about the presence of an analyte and semi-quantitative information about the amount of material present.

Level I methods quantify the amount of a specific analyte or class of analytes and positively identify the analyte, providing the greatest amount of reliability for quantitation and structure identification of the analyte at the level of interest. These methods may be a single procedure that determines both the concentration and identity of the analyte, or a combination of methods to quantify and confirm the structure of a veterinary drug residue. A good example of the latter is a chromatographic technique combined with a mass spectrometry procedure. Although Level I methods are generally instrumental procedures, observation of a pathologic or other morphologic change that specifically identifies exposure to a class of veterinary drugs, could potentially be a Level I method, if it has sufficient sensitivity and precision.

Level I methods may be limited to analytes with appropriate physical and chemical properties amenable to chromatographic and other instrumental methods of analysis. For example, at the present time, there are very few antibiotic drugs for veterinary use that have mass spectrometric procedures useful to determine compliance with MRLVDs because of the relatively low volatility and stability of

antibiotic drugs to chemical techniques commonly employed for mass spectrometry analysis. However, new technology and instrumentation is now making development of these confirmatory methods possible. Level I methods are sometimes referred to as reference methods.

Level II methods commonly determine the concentration of an analyte at the level of interest, but do not provide unequivocal structure identification. These methods may use structure, functional group, or immunological properties as the basis for the analytical scheme. A common practice is to use one Level II method as the determinative assay and a second Level II method as the positive identification procedure. These methods may also be used to verify the presence of a compound or class of compounds. Two Level II methods may provide information suitable for a Level I method, when they use different chemical procedures. The majority of analytical methods commonly used to support MRLVDs are quantitative Level II laboratory methods.

Level III methods are those that generate less definitive but useful information. These testing procedures generally determine the presence or the absence of a compound or class of compounds at some designated level of interest. They are often based on non-instrumental techniques. For these reasons, Level III methods are commonly referred to as screening or semi-quantitative methods. Results on a given sample are not as reliable as Level I or II methods and usually need corroborating information for regulatory action. For example, Level III methods may provide good semi-quantitative information, but poor identification. Alternatively, they may provide strong or unequivocal identification with very little quantitative information. Level III methods are not poorly described or sloppy methods. They must have a well-defined operating protocol, operating characteristics and performance data.

Many of the microbiological agar plate assay procedures, enzyme inhibition assays and immunology based systems are in this category. They are useful for residue control programmes because of their high sample capacity, portability, convenience and potential suitability to non-laboratory environments. The limitation of Level III type methods is that action based on individual positive results usually requires verification using Level I or II methods. Individual results may be verified by epidemiological information.

Level III methods may offer substantial advantages to a residue control programme. Their advantages include analytical speed, sample efficiency through batch analysis, portability to non-laboratory environments, good sensitivity, or the ability to detect classes of compounds. Even though a Level III method may not detect a specific compound at a regulatory limit (i.e., an MRLVD) with every sample, it may be better than relying on Level I and II methods because of their ability to test more samples.

The decision to use Level III methods should be determined in part by performance characteristics, as well as the need to test large numbers of samples within a given time frame. Two key characteristics to consider for Level III methods are the percent false positives and percent false negatives, determined by comparison with a validated quantitative assay in a statistically designed protocol. The percent false negatives must be quite low at the levels of interest, while slightly more flexibility may be acceptable for false positives. Residue detection limits can be described based on these two parameters.

METHOD ATTRIBUTES

Specificity is the ability of a method to distinguish between the analyte being measured and other substances which may be present in the test material. A proposed method also must provide the required specificity for the compound being measured and discriminate between other structurally similar substances. This characteristic is predominately a function of the measuring principle or detection system used. Certain instrumental techniques such as Fourier transform infrared

spectroscopy or mass spectrometry may be sufficiently specific by themselves to provide unambiguous identification. These are often referred to as confirmatory methods. Positive identification from a confirmatory method is usually considered necessary before regulatory action is taken in those instances when an analytical result is not sufficiently specific for regulatory purposes. Confirmatory methods may be considered Level I methods when they provide a determinative result to quantify and tentatively identify a given analyte, and a procedure which verifies the identity of the analyte of interest.

Other techniques, when they are used in combination, may be capable of achieving a comparable degree of specificity as confirmatory techniques. For example, specificity may be verified by combinations of methods such as thin layer chromatography, element-specific gas-liquid chromatography and accompanying detection systems, formation of characteristic derivatives followed by additional chromatography, or determining compound specific relative retention times using several chromatographic systems of differing polarity. Such procedures must be applicable at the designated maximum residue limit (MRLVD) of the analyte.

The specificity of a screening method normally is not as great as that of a determinative method, because screening methods often take advantage of a structural feature common to a group or class of compounds. These methods generally fit into the Level III methods category. Techniques based on biological assays, immunoassays, or chromogenic responses are not expected to be as specific as those techniques which unequivocally identify a compound. Specificity of a screening method may be increased by the use of chromatographic or other separation technique.

If a non-specific response or some ambiguity in a test result is obtained (i.e., cross-reactivity with components of the matrix other than that for which the analysis was designed), studies that approximate the concentration of the non-specific response of the analytical method may be required to identify the compounds that respond to the detection system. If the method is not sufficiently specific, then a confirmatory or identification procedure will be needed to characterize the analyte of interest.

Precision is an important performance characteristic of residue control methods. This attribute is common to all methods, and as noted below, acceptable precision may not be a function of the type of method, but of the concentration of the analyte in the original sample. There are several types of precision. Inter-laboratory precision, or reproducibility, is the closeness of agreement between test results obtained with the same method on identical test material in different laboratories. The variation in replicate analyses of a test material within a laboratory when performed by one analyst is repeatability. The intra-laboratory variability among analysts performing the same analysis is within-laboratory bias, and is primarily due to random error. Precision is usually expressed as a standard deviation (an absolute value determined experimentally). More useful is the relative standard deviation, or coefficient of variation. This parameter expresses variability as a function of concentration, and is relatively constant over a given concentration interval.

Precision limits for analytical methods, as a function of concentration, are presented below. The recommended values take into consideration the wide variety of methods, analytes, matrices, and species within the terms of reference of the Committee and that are usually applied in a broad-based residue control programme.

Concentration	Coefficient of Variability (CV) (Repeatability)
$\leq 1 \mu\text{g/kg}$	35%
$\geq 1 \mu\text{g/kg} \leq 10 \mu\text{g/kg}$	30%
$\geq 10 \mu\text{g/kg} \leq 100 \mu\text{g/kg}$	20%
$\geq 100 \mu\text{g/kg}$	15%

The variability achieved in the laboratory where a method was developed, and where there is considerable experience, is usually smaller than that attained by laboratories that may later use the method and have less experience with it. The final version of the method should be optimized by using procedures such as ruggedness testing to identify its critical control points and ensure that its performance will not be adversely affected by small changes in using the analytical procedure. If a method cannot achieve acceptable performance in the sponsor's laboratory, its performance usually will not be any better in other laboratories.

When developing analytical data to be used to define expected method variability and other performance characteristics, methods should be performed by an analyst who has not been directly involved in developing the method. This procedure will verify the adequacy of the method's written description and help identify critical parameters which affect method performance.

The within laboratory coefficient of variation should be ≤ 15 percent when the designated concentration of the analyte is greater than or equal to $100 \mu\text{g/kg}$. When the designated concentration of the analyte is $10 - 100 \mu\text{g/kg}$, the within laboratory coefficient of variation should be ≤ 20 percent. When the concentration of interest is below $10 \mu\text{g/kg}$, a coefficient of variation of ≤ 30 percent is acceptable.

A Level III method should be capable of identifying samples that contain a residue concentration at the level of interest. When a sample contains a residue that exceeds the MRLVD using a semi-quantitative (screening) method, regulatory action requires additional analysis. In this situation, the sample will require analysis using a determinative method and a confirmatory method with defined performance characteristics. A useful attribute for Level III methods is its precision at and just below the MRLVD. Precision may be somewhat less important above the MRLVD.

Systematic error, or method bias, is the difference between the experimentally determined (measured) value and the mean result that would be obtained by applying the experimental procedure a very large number of times to the test material. Systematic errors are always of the same sign and magnitude. Random error, however, is variable in magnitude and sign and the mean of random errors may approach zero if sufficient samples are tested. Accuracy is generally expressed as the percent recovery of the analyte of interest. Recovery is obtained experimentally by adding known quantities of the analyte directly to separate portions of the test material and comparing the amount recovered with the amount added. The percent recovery of an analyte added directly to the sample matrix is generally a higher value than is obtained experimentally when isolating the same biologically incurred analyte from a given sample matrix. At relatively high analyte concentrations, recoveries are expected to approach 100 percent. At lower concentrations or with multi-step methods that require extractions, solvent transfers, concentration steps, and absorption chromatography, recoveries will be lower. Variability of analyte recovery is usually as important as the percent recovery itself and should be small.

Average recoveries of 80 to 110 percent should be obtained when the MRLVD for the analyte is $100 \mu\text{g/kg}$ or greater and when the analytical method can be performed with acceptable precision.

Recommended acceptable recoveries at lower MRLVDs are 70 to 110 percent when the MRLVD is 10 µg/kg to 100 µg/kg, and 60 to 120 percent when the MRLVD is less than 10 µg/kg. These recovery limits are reasonable when viewed within the context of the wide variety of residues, methods, matrices, and species normally included in a broad-based residue testing programme. Variability in recovery should be small regardless of the percent recovery.

Correction factors for more or less than 100 percent recovery may be appropriate when analytical methods use isotope dilution procedures or other appropriate internal reference standards for quantitation purposes.

The accuracy requirements of different types of methods will vary with the intended use for the results. In general, methods should have their greatest accuracy at the MRLVD. The accuracy requirements of confirmatory methods may not be as great as is required for quantitative methods, because in most residue control programmes these methods are only performed after a residue concentration greater than the MRLVD has been determined by a quantitative method. Most confirmatory methods have a quantitative aspect built into them which serves as an additional check on the previously performed quantitative method. Suggested accuracy requirements for methods are given below, and are based upon the previously stated considerations of a broad-based residue testing programme.

Concentration	Acceptable range
≤ 1 µg/kg	-50 to +20%
≥ 1 µg/kg ≤ 10 µg/kg	-40 to +20%
≥ 10 µg/kg ≤ 100 µg/kg	-30 to +10%
≥ 100 µg/kg	-20 to +10%

Level III methods may be useful for residue control programmes in several scenarios. For example, they may be used in situations where no MRLVD can be established or where one does not otherwise exist, and regulatory action may be taken if any amount of the drug residue is found. Non-quantitative methods may also be used when the MRLVD or the level of interest is less than the limit of detection of the screening method. In both cases, it is necessary to evaluate proposed methods for the specified residue test to experimentally determine the lowest concentration at which an analyte can be detected and to determine method accuracy and limits by using data on false negatives (i.e., a negative analytical result is obtained when the analyte is present), and false positives, (i.e., a positive result is obtained when the analyte is not present) at or above the MRLVD.

If Level III methods involve a manufactured test kit, at a minimum, the accuracy, precision, specificity and lowest detection limit data should be provided by the manufacturer. The users should verify the validity of this data through their own studies and evaluate performance by quality control checks. The lowest detectable concentration of an analyte should represent the smallest amount of an individual analyte that can be reliably observed or found in the test sample. The method accuracy, expressed in terms of false negatives and false positives, should be determined by a statistically valid, scientifically correct study with appropriate controls.

In general, non-quantitative methods should produce less than 5 percent false negatives and less than 10 percent false positives when analysis is performed on the test sample. These values may vary depending on the type of action that will be taken as a result of the analytical test. Conservative values should be chosen appropriate to residue testing needs.

The limit of detection is the smallest measured concentration of an analyte from which it is possible to deduce the presence of the analyte in the test sample with acceptable certainty. This determination should consider matrix related interferences with an instrumental signal to noise (S/N) ratio greater than 5:1 or the concentration determined by a factor of 3 standard deviations of the signal response for blank tissue, whichever is less.

Sensitivity is a measure of the ability of a method to detect the presence of an analyte and to discriminate between small differences in analyte content. This may be determined by the slope of the standard curve at concentrations of interest.

COLLATERAL PARAMETERS FOR METHODS SUITABLE FOR ROUTINE USE FOR ENFORCEMENT OF MAXIMUM RESIDUE LIMITS

Residue control methods should be capable of analyzing several samples simultaneously, normally in groups of four or more during a normal work period. These methods should ideally require no more than about 2 hours of analytical time per sample. This does not require that results for a set of analytical samples must be completed within 2 hours. Several hours may be necessary to prepare a set of extracts or complete a microbiological incubation, for example, before analysis of test sample results can be completed. Regulatory methods should be able to be completed within reasonable time periods consistent with regulatory objectives.

The applicability of a method refers to the tissue matrices and animal species that a particular method has demonstrated acceptable method performance for compliance with an MRLVD.

The limit of quantitation corresponds to the smallest measured concentration of residue from endogenously incurred test material above which a determination of the analyte can be made with a specified degree of certainty to its accuracy and precision.

For determining compliance with an MRLVD, an analytical method should require only instrumentation generally available in a laboratory devoted to trace analyses in the appropriate test material. The methods should be capable of analyzing analytes at or below the MRLVD. In addition, the methods should have written protocols that include extensive quality assurance and quality control components. These quality assurance plans should also include analyst training needs.

Whenever applicable, methods should be evaluated in an inter-laboratory study using some test samples with biologically incurred analyte. Experience suggests that using biologically incurred residues for method evaluation provides a better description of the expected performance characteristics of the method as it would be used routinely by regulatory authorities.

Residue testing methods must demonstrate that they can be performed at their described performance characteristics by experienced analysts who have received adequate method training. Acceptable methods performance can be demonstrated by successfully analyzing sets of samples containing the analyte of interest in sample matrices within the scope of the CCRVDF terms of reference.

Methods to determine compliance with MRLVDs should utilize commercially available reagents and equipment. Methods may become impractical and potentially unreliable if new or unusual reagents are not readily available. New or unusual reagents and standards must be assured by the method sponsor upon request.

Regulatory methods for residue control should not use large quantities of solvents, reagents, and supplies which would render the method economically impractical. Methods for determining compliance with Codex MRLVDs should be designed for safe performance by trained analysts.

Several other indicators of satisfactory performance may be helpful in determining whether or not a method is acceptable for Codex purposes. These include: (a) calibration (standard) and analytical (recovery) curves; (b) information on the effectiveness of extraction for removing specific potential interferences; (c) adequate method sensitivity (slope of the standard calibration curve) with a linear dynamic range at the concentration of interest; (d) adequate resolution from matrix components; (e) sufficiently low and reproducibly consistent blanks; and (f) stability studies performed on the matrix, the analyte within the matrix, and reagents used in the procedure. The analytical response of the blank should be no more than 10% of the analyte response at the MRLVD, whenever an MRLVD is established. Critical control points within the analytical procedure, those steps where extreme care must be taken to insure optimum method performance, and stopping points within the method need to be identified and noted in the written procedure.

SPECIFIC DATA NEEDED

The developer of a method must provide pertinent information and supporting data necessary to familiarize other intended users of a method so they can achieve satisfactory methods performance. This necessary information should include the following:

For Codex methods, the developer of a method should collect and provide data from three types of samples: (a) control tissue samples from animals that are known not to have been exposed to the analyte; (b) tissue samples that are fortified or spiked at the levels of interest by the addition of known amounts of the analyte to uncontaminated control tissue; and (c) dosed or incurred tissue samples at the concentration of interest (MRLVD) obtained from animals treated with the veterinary drug according to good veterinary practices.

Methods provided by developers, drug sponsors and commercially available test kits intended for use with Codex MRLVDs should only be recommended for use after it can be demonstrated that the method(s) will meet established performance characteristics or provide an improvement to current methods, regulatory decision making and regulatory consistency.

The developer of the method must determine: (a) the analytical response obtained when the matrix is known to be free from chemical interferences; (b) the method variability, and (c) the lowest concentration at which the amount of analyte present can be detected with reasonable statistical certainty. The data should demonstrate that the proposed method can satisfactorily recover and identify known amounts of the analyte that have been added to the test sample. Finally, the developer should demonstrate that the proposed method can satisfactorily recover the analyte from the target tissue matrix in which it has been biologically bound or incurred. Recovery studies must demonstrate absence of responses from substances that may interfere or adversely affect the reliability of the analysis.

The method must demonstrate acceptable method performance in controlled laboratory environments and in field trials which represent anticipated operating conditions, if that is the intended use of the method. The results must be verified by appropriate quality assurance and quality control procedures, including analysis of known blank and positive control samples. Analysis of sufficient numbers of both positive and negative control samples must be performed to establish false positive and false negative rates, with a statistically appropriate number of these samples analyzed by a separate method to verify the results.

A complete description of the method must be provided which includes the scientific principle(s) upon which the method is based, preparation of analytical standards, appropriate tissues the method is suitable for, shelf-life and storage conditions for the analyte in solution and in the target tissue matrix, reagent and standard shelf-life stability, instrumentation as well as their performance

standards and calibration procedures, and identification of critical steps and stopping places. Test limitations as well as appropriate and inappropriate uses of the test must be described. Critical test components and reagents must be identified and specifications described. The developer must provide procedures for demonstrating evidence of satisfactory method performance as well as guarantee the long term availability of all components necessary to successfully perform the test.

For rapid test procedures, the quality control criteria needed to verify and maintain acceptable method performance and to determine that a test kit is operating properly must be provided. Information to verify proper test data interpretation associated with the quality control criteria must be specified. A standard curve prepared for the analyte of interest of known purity is needed. A typical analytical curve prepared by fortifying blank test material with the analyte of interest must be provided.

Data from uncontaminated, fortified, and dosed test material is required to show that the method meets the specificity, precision, systematic error, and accuracy attributes for its intended use. Test samples should be fortified at 0.5 (where practical), 1 and 2 times the MRLVD. Additional samples within these concentration limits may be included.

Data from inter-laboratory studies should be provided on the analytical worksheet developed for evaluating methods for Codex MRLVDs. The method should be tested in three or more laboratories for ease in evaluating multi-laboratory study reports. Each laboratory should analyze samples fortified as stated previously and should test biologically incurred samples containing the analyte at the same concentrations.

Test kits should utilize simple, unambiguous procedures. The analytical procedures designed into test kits to be used by field personnel should be successfully evaluated by at least ten trained individuals in a properly designed study before being placed into general use. The study environment must be similar to that expected for routine use of the test. The design should provide sufficient data for a statistical description of false positive and false negatives, and allow determination of the analytical limits of the test. Participants should include those individuals who have been trained by the developer of the test to determine that training procedures are sufficient to provide acceptable method performance.

STANDARD REFERENCE MATERIALS FOR VETERINARY DRUG RESIDUE ANALYSIS

At the present time it is usually not practical to develop standard reference materials for determination of residues of veterinary drugs in foods. There are specific difficulties in developing standard reference materials for international use as noted below.

Some drugs are not sufficiently stable in test materials at ordinary freezer temperatures. Veterinary drug residue concentrations commonly deplete with time, dependent upon the analyte and test material, at ordinary freezer temperatures. These test materials must be stored and shipped at ultra-cold temperatures or use lyophilized, irradiated, or treated otherwise to reduce enzymatic activity and prevent loss of analyte. The relevant studies for most compounds of interest to CCRVDF have not been published at this time, so it is not known whether treatments noted above will affect the extent to which the drugs of interest are bound to the tissues, whether drug residues remain stable in tissues, or whether they might chemically alter the trace residues.

Recognized standard reference materials are generally very expensive and, considering their other limitations, they are generally not cost effective for residue analysis. Commercial reference standards for veterinary drugs have limited availability at the present time. Because of these and other limitations, such as analytical variability of a method versus the concentration of the analyte (i.e., low mg/kg to µg/kg), standard reference materials are generally inappropriate.

ANNEX 11

Melengestrol acetate (CCRVDF chronology)

CCRVDF (session)	Discussion/Status
11 th CCRVDF (1998)	Added melengestrol acetate (MGA) to the priority list for evaluation or re-evaluation at the 54 th JECFA. ²⁷
12 th CCRVDF (2000)	Agreed to not consider the recommendations of the 54 th JECFA. ²⁸
13 th CCRVDF (2001)	Advanced the temporary MRL for MGA to Step 5 and noted that MGA was scheduled for re-evaluation by the 58 th JECFA for a practical analytical method for monitoring residues at the recommended MRL. ²⁹
14 th CCRVDF (2003)	Decided to retain the MRLs at Step 6 and requested JECFA re-evaluation based on new information and additional data to be submitted. ³⁰
15 th CCRVDF (2006)	Was informed of an inaccuracy in the calculation of the TMDI for MGA and decided to request JECFA to reassess the recommended MRLs from the 62 nd JECFA and to circulate for comments at Step 6 the MRLs from the 66 th JECFA for consideration at its next session. ³¹
16 th CCRVDF (2006)	Considered the MRLs for MGA recalculated by the 66 th JECFA. However, because of the lack consensus on the further advancement of the MRLs, the Committee agreed to retain the MRLs at Step 7 for further consideration at its next session (scheduled in 2007). ³²

²⁷ ALINORM 98/31, para 121 and Appendix VIII.

²⁸ ALINORM01/31, para. 61.

²⁹ ALINORM 03/31, para 43.

³⁰ ALINORM 03/31A, paras 48 and 113 and Appendix VII.

³¹ ALINORM 05/28/31, paras 61-62.

³² ALINORM 06/29/31, para. 73, Appendix III.

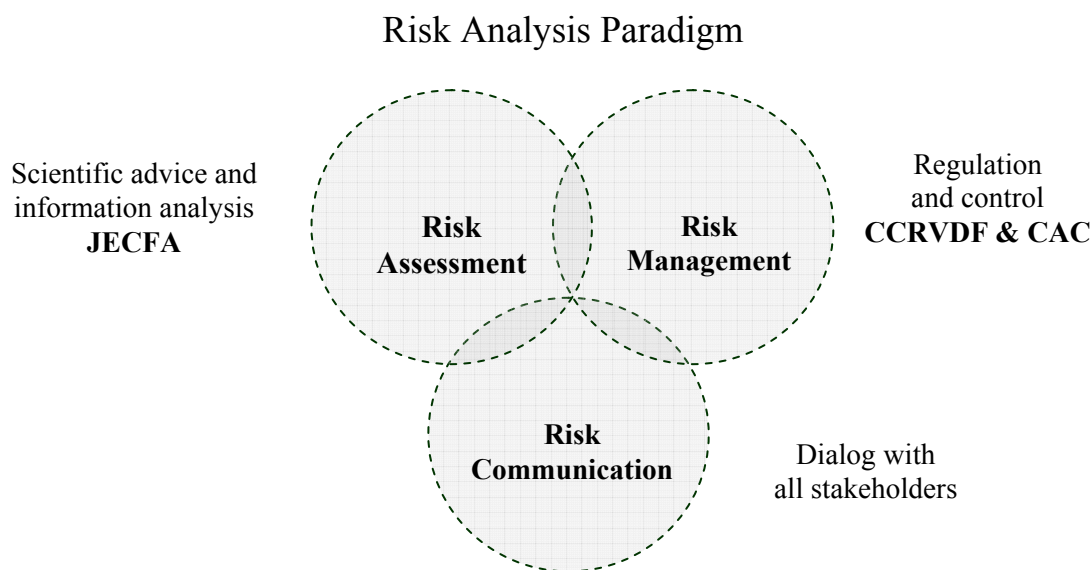
ANNEX E-2

REPLIES OF THE JOINT FAO/WHO JECFA SECRETARIAT TO CERTAIN QUESTIONS POSED BY THE PANEL TO INTERNATIONAL ORGANIZATIONS

Introduction

Risk Analysis is a process consisting of three components: risk assessment, risk management and risk communication. Risk management activities for veterinary drugs within Codex are carried out by the CCRVDF, which prepares draft standards, guidelines and recommendations for consideration by the CAC. Risk assessment activities are performed by JECFA, which is an independent scientific expert body, which advises CCRVDF, but also Members and WHO and FAO directly. JECFA provides independent advice and as such is not part of Codex. Risk communication is the responsibility of all involved parties. JECFA has provided scientific advice on veterinary drug residues since 1982. The separation of tasks is illustrated in the graph below.

Annex 1 gives a brief fact sheet on JECFA, which has been meeting since 1956, i.e. it predates Codex.



3. Please identify any international guidance documents relevant to the conduct of a risk assessment with respect to veterinary drug residues. Since when have they been available? Please also indicate if there is any relevant ongoing work at Codex.

The elaboration and application of risk assessment principles are within the responsibility of the scientific expert bodies. Codex bodies elaborate risk assessment policies as they relate to their respective areas of work for the risk assessment bodies in terms of the respective roles and tasks and general guidance on the type of scientific advice requested.

The following lists the key international risk assessment documents relevant to the assessment of veterinary drug residues in food:

- The basis for JECFA risk assessments of veterinary drug residues in food: Environmental Health Criteria 70: Principles for the Safety Assessment of Food Additives and Contaminants in Food, World Health Organization, Geneva 1987. <http://www.inchem.org/documents/ehc/ehc/ehc70.htm>. Subsequently, these principles have been further elaborated, clarified and updated in JECFA meetings dealing with veterinary drug residues in food. These agreed updates are reported under 'General Considerations' in each report. This is a continuing effort to have up-to-date risk assessment principles and methods applied. These principles have been developed over the years of evaluation of different chemical substances, including veterinary drugs.
- Consolidation of all these principles and harmonization between the assessment of veterinary drug residue and pesticide residue, to the extent useful, within the 'Project to update the principles and methods for the assessment of chemicals in food', to be published by the end of 2006. <http://www.who.int/ipcs/food/principles/en/>
- Principles and methods for the derivation of maximum residue limits of veterinary drugs in food as elaborated by JECFA have been compiled in a format easily accessible to the public in the following document: Procedure for recommending maximum residue limits – residues of veterinary drugs (2000) ftp://ftp.fao.org/es/esn/jecfa/2000-06-30_JECFA_Procedures_MRLVD.pdf
- The data requirements for the assessment of the residues of veterinary drugs have been detailed by the Committee at the 32nd (1987) and 42nd (1994) meetings. These are contained in the above publication. Furthermore, a more complete description of these procedures is available from a recent expert FAO/WHO/RIVM workshop on the update of principles and methods of risk assessment: Maximum Residue Limits (MRLs) for pesticides and veterinary drugs (report available at the following website ftp://ftp.fao.org/ag/agn/jecfa/bilthoven_2005.pdf).
- Several other documents regarding various aspects for the risk assessment of chemicals as developed and published by the International Program on Chemical Safety, in particular (but not exclusively):
 - Guidance values for health-based exposure limits. Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits (EHC No 170, 1994) <http://www.inchem.org/documents/ehc/ehc/ehc170.htm>
 - Biomarkers In Risk Assessment: Validity And Validation, Environmental Health Criteria 222, 2001. <http://www.inchem.org/documents/ehc/ehc/ehc222.htm>
 - IPCS Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis. Regulatory Toxicology and Pharmacology Volume 34 (2001) 146-152. <http://www.who.int/ipcs/publications/methods/harmonization/en/index.html>
 - Harmonization Project Document No. 2, Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment, WHO, Geneva 2005. http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf
 - Guidance on acute reference dose setting. Food and Chemical Toxicology 43 (2005) 1569–1593 http://www.who.int/ipcs/food/jmpr/arfd_guidance.pdf

All these documents are the outcome of international expert meetings and represent the agreed views of the participating experts and several of those have also been published in the scientific literature. There is a continuous effort to update and harmonize on an international level risk assessment methodologies for chemicals.

4. The European Communities states that there is "no Codex standard specifically on the risk assessment of effects of residues of veterinary drugs" but a general one on microbiological assessment. Is this correct? Which guidelines or principles have been used by JECFA in the conduct of its risk assessments with respect to the hormones at issue? [see para. 192 of EC Rebuttal Submission (US case)]

As outlined under question 3 above, the elaboration and application of risk assessment principles are within the responsibility of the scientific expert bodies. Regarding the principles for the risk assessment of chemicals in food, including of veterinary drug residues in food, please refer to the list of international risk assessment guideline documents above.

6. Please briefly describe the four steps of a risk assessment (hazard identification, hazard characterization, exposure assessment and risk characterization) as identified by Codex, indicating any relevant sources.

Risk assessment comprises of four steps, as defined by many national and international bodies:

Hazard identification: identification of potential adverse health effects as inherent property of a compound.

Hazard characterization: includes dose-response assessment, considerations on species sensitivity, relevance of specific effect for humans etc.

Exposure assessment: estimation of dietary intake

Risk Characterization: integration of the hazard characterization and exposure assessment for a qualitative or quantitative estimate of risk.

Main reference: Application of risk analysis to food standards issues: report of the Joint FAO/WHO Expert Consultation, 1995.

7. Please comment on the EC statement made in para. 140 of the EC Replies to Panel Questions that "which ever approach of a risk assessment is followed, they are all based on a deterministic approach to risk characterization [and that they] have serious limitations in non-linear situations, such as in the current case regarding hormones". Are these situations addressed by the risk assessment guidance currently available from the Codex Alimentarius Commission? [see Canada's comments in para. 72 of its Rebuttal Submission]

There are no risk assessment guidelines available from the Codex Alimentarius Commission, which applies to the assessment principles and procedures of JECFA. JECFA is an expert committee which has been called into existence by the Director Generals of FAO and WHO. The constitutions and rules of both organizations for such committees are in particular considered in Article VI of the Constitution of FAO and the Regulations for Expert Advisory Panels and Committees of WHO lay down the basic rules which assure excellence and independence of expert committees which provide scientific advice to both organizations.

Throughout its existence JECFA has continued to develop principles for the safety assessment of chemicals in food (see answer to question 3 above).

In general, most risk assessments of chemicals today on a national and international level are deterministic, i.e. they use a point estimate for the toxicological endpoint and a point estimate for the exposure assessment. This is not considered a limitation of the risk assessment process, but often a necessity due to the information at hand. Uncertainties around these point estimates should be considered in the risk assessment process. The current risk assessment process, which includes consideration of sensitive subpopulations, is considered to be sufficiently conservative to be public health protective.

Increasing efforts are under way, also within the International Program on Chemical Safety, to explore methods to perform probabilistic risk assessment, i.e. include distributions rather than point estimates in the risk assessment process. In the area of exposure assessment probabilistic methods have been developed and are increasingly applied, also by JECFA, however probabilistic methods in the toxicological assessment are not yet internationally agreed and are not yet commonly applied. Moreover, the outcome of a probabilistic risk assessment is much more difficult to interpret and apply by risk managers.

Probabilistic or deterministic approaches can be applied, independent if a compound is assumed to act via a threshold mechanism, i.e. non-linear, or not. JECFA's assessment process is based on the mechanism of action of the compound to be evaluated, non-linearity is assumed if the adverse effect of a compound is caused via a mechanism with a threshold of effect. In such a case, as for the hormones, a no-effect-level can be determined from which an ADI can be established.

JECFA has in its reports and in the toxicological monographs on the safety assessment of the hormones used risk assessment principles particularly targeted to the evaluation of such substances. JECFA has distinguished between hormones that are identical to those occurring naturally in food-producing animals and human beings, i.e. endogenously produced hormones and substances with hormonal activity, which are either synthetic or naturally occurring but which are not identical with human endogenous hormones. As is standard practice, all toxicological effects of the hormones have been considered by JECFA in the risk assessment, including the hormonal no-effect-levels (the dose at which no effects are found) and other relevant toxicological end-points, such as reproductive toxicity, genotoxicity and potential carcinogenicity. The conclusion of the risk assessments are detailed in the respective report and monographs of JECFA.

8. Do JECFA or Codex materials confirm Canada's statement in para. 80 of its Rebuttal Submission that "... while international risk assessment techniques suggest that a dose-response assessment is optional for biological or physical agents when the data cannot be obtained, a dose-response assessment should always be conducted for chemical agents ..."? [see Exhibit CDA-25]

Dose-response assessment is an integral part of each assessment and is an essential part of the hazard characterization step. This can be done in a quantitative or a qualitative way. In the qualitative sense this is the determination of a no-effect-level (NOEL or NOAEL) from an experimental or epidemiological study. For the hormones JECFA used this approach. In some cases, for contaminants (e.g. aflatoxins), JECFA has applied a quantitative dose-response assessment.

The International Programme on Chemical Safety (IPCS) has recently held an international workshop to further elaborate the principles of dose-response assessment. The final report will be published in the Environmental Health Criteria Series: Principles for Modelling Dose-Response for the Risk Assessment of Chemicals. Specifically as relevant to chemicals in food, part of the report will also be included in the updated principles document on the risk assessment of chemicals in food (see under question 3). The draft report was made available for public comment, and is accessible under: http://www.who.int/ipcs/methods/harmonization/draft_document_for_comment.pdf

9. Please provide definitions for the following terms: Acceptable Daily Intake (ADI) and Maximum Residue Limit (MRL).

ADI: acceptable daily intake: An estimate of the amount of a substance in food or drinking water, expressed on a body-weight basis, that can be ingested daily over a lifetime without appreciable risk (standard human = 60 kg). The ADI is listed in units of mg per kg of body weight.

Source: JECFA glossary of terms: <http://www.who.int/ipcs/food/jecfa/glossary.pdf> (based on EHC 70)

ADI: Estimated maximum amount of an agent, expressed on a body mass basis, to which individuals in a (sub)population may be exposed daily over their lifetimes without appreciable health risk.

Related terms: *Reference dose*, *Tolerable daily intake*

Source: IPCS Risk Assessment Terminology

<http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf>

MRL: Residues of veterinary drugs is defined as follows in the Procedural Manual of the Codex Alimentarius Commission: Residues of veterinary drugs include Parent compounds and/or their metabolites in any edible portion of the animal product, including associated impurities of the veterinary drug concerned, which may be of significance to human health. On a recommendation to harmonize the definitions of residues of veterinary drugs and pesticides from the conclusions of the FAO/WHO workshop on updating the principles and methods of risk assessment: MRLs for pesticides and veterinary drugs (see answer to question 3 above), a modified definition was adopted by the 66th meeting of JECFA as follows: Parent compounds and/or their metabolites, including associated impurities of the veterinary drug concerned, in any edible portion of the animal product, which may be of significance to human health.

10. Please describe the procedure followed by JECFA in the identification of ADIs and the development of recommendations on MRLs. Please also identify and describe any steps that are taken in the risk assessment process to build a margin of safety into to the final recommendation.

Establishment of ADI

Source: EHC 70:

5.5. Setting the ADI

Almost any substance at a high enough test level will produce some adverse effect in animals. Evaluation of safety requires that this potential adverse effect be identified and that adequate toxicological data be available to determine the level at which human exposure to the substance can be considered safe.

At the time of its first meeting, JECFA recognized that the amount of an additive used in food should be established with due attention to "an adequate margin of safety to reduce to a minimum any hazard to health in all groups of consumers" (9, pp. 14-15). The second JECFA, in outlining procedures for the testing of intentional food additives to establish their safety for use, concluded that the results of animal studies can be extrapolated to man, and that

"some margin of safety is desirable to allow for any species difference in susceptibility, the numerical differences between the test animals and the human population exposed to the hazard, the greater variety of complicating disease

processes in the human population, the difficulty of estimating the human intake, and the possibility of synergistic action among food additives" (10, p. 17).

This conclusion formed the basis for establishing the "acceptable daily intake", or ADI, which is the end-point of JECFA evaluations for intentional food additives. In the context in which JECFA uses it, the ADI is defined as an estimate (by JECFA) of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk.

The ADI is expressed in a range, from 0 to an upper limit, which is considered to be the zone of acceptability of the substance. JECFA expresses the ADI in this way to emphasize that the acceptable level it establishes is an upper limit and to encourage the lowest levels of use that are technologically feasible.

Substances that accumulate in the body are not suitable for use as food additives (39, p. 8). Therefore, ADIs are established only for those compounds that are substantially cleared from the body within 24 h. Data packages should include metabolism and excretion studies designed to provide information on the cumulative properties of food additives.

JECFA generally sets the ADI of a food additive on the basis of the highest no-observed-effect level in animal studies. In calculating the ADI, a "safety factor" is applied to the no-observed-effect level to provide a conservative margin of safety on account of the inherent uncertainties in extrapolating animal toxicity data to potential effects in the human being and for variation within the human species. When results from two or more animal studies are available, the ADI is based on the most sensitive animal species, i.e., the species that displayed the toxic effect at the lowest dose, unless metabolic or pharmacokinetic data are available establishing that the test in the other species is more appropriate for man (section 5.5.1).

Generally, the ADI is established on the basis of toxicological information and provides a useful assessment of safety without the need for data on intended or actual use and consumption. However, in setting ADIs, an attempt is made to take account of special subpopulations that may be exposed. Therefore, general information about exposure patterns should be known at the time of the safety assessment (section 5.5.6). For example, if a food additive is to be used in infant formulae, the safety assessment is not complete without looking carefully at safety studies involving exposure to very young animals.

JECFA uses the risk assessment process when setting the ADI, i.e. the level of "no apparent risk" is set on the basis of quantitative extrapolation from animal data to human beings.

The above described procedure and principles are equally applied to residues of veterinary drugs by JECFA.

Establishment of the ADI follows the following steps:

- determination of a no-observed-effect level
- application of safety factors

A safety factor has been used by JECFA since its inception. It is intended to provide an adequate margin of safety for the consumer by assuming that the human being is 10 times more sensitive than the test animal and that the difference of sensitivity within the human population is in a 10-fold range.

In determining an ADI, a safety factor is applied to the no-observed-effect level determined in an appropriate animal study.

JECFA traditionally uses a safety factor of 100 (10 x 10) in setting ADIs based on long-term animal studies, i.e., the no-observed-effect level is divided by 100 to calculate the ADI.

Deviation from the default safety factor can be considered when e.g. the inadequacy of database may justify a larger safety factor, or when a no-observed effect level is derived from adequate human data a smaller safety factor may be applied. Moreover, recently the concept of chemical specific adjustment factors (CSAF) has been applied if appropriate data were available. (Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment, WHO, Geneva 2005. http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf)

Residue evaluation:

Derivation and recommendation of maximum residue limits (MRLs)

JECFA has specified the data requirements that are intended to adequately identify and characterize the veterinary drug being evaluated for toxicology and residue considerations. Specific information is requested on mode of administration, dose and formulation, pharmacokinetic, metabolic and pharmacodynamic studies, residue depletion studies with radiolabelled drug and non-radiolabelled drug in target animals at appropriate times of withdrawal, information on major residue components for determining a marker residue and target tissue. In addition, information is requested regarding free and bound residues (including bioavailability), routine analytical methods and appropriate method performance factors and information on antimicrobial assays for those compounds for MRL considerations on antimicrobial end points. The above data are requested for all relevant food animal species and tissues, as well as milk, eggs and honey using good veterinary practice. The JECFA has developed a mathematical model to account for bound residues in tissue. In consideration of MRLs, the JECFA also reviews the comparative metabolism between laboratory animals and food animals to determine qualitative or quantitative similarities or differences in metabolites across species.

The JECFA does not recommend MRLs when the theoretical maximum daily intake (TMDI) of residues substantially exceeds the ADI. The TMDI is the upper limit consideration in recommending MRLs. For purposes of recommending MRLs, the JECFA uses a theoretical food basket that consists of 300 g muscle, 100 g liver, 50 g kidney, 50 g fat, 1500 g milk, 100 g for eggs and 20 g for honey. Considerations in MRLs are based on the adequacy of the data. Where a large database is available, statistical approaches to MRLs may be used.

JECFA uses radiolabelled parent drug studies in intended host animal species as well as additional studies with non-radiolabelled parent drug for recommending MRLs and a marker residue compound and appropriate target tissues for residue analysis. Dose treatments preferably considered are those conducted at the maximum approved dose. Residues are generally determined in all four edible tissues – muscle, liver, kidney and fat as well as milk and eggs, where the data are sufficient. JECFA identifies the appropriate stable compound that can be used as the marker residue and indicates the most appropriate tissues for analysis, considering needs of national authorities for domestic residue control programs and product intended for international trade. These studies also provide the necessary information to determine consideration of bound residues and relationships between the marker residue and total residues of concern as determined by the ADI.

JECFA has recognized that the use of veterinary drugs in food producing animals can result in residues that are neither extractable from tissue nor readily characterized using mild extraction procedures. The Committee has developed a procedure to estimate the maximum daily intake of

residues of a drug that has a bound residue component. It takes into account the toxicological potency and bioavailability of the residues.

$$\begin{aligned}\text{Residues} &= \text{Free residues} + \text{Bioavailable bound residues.} \\ \text{Bound residue} &= \text{Total residue} - (\text{extractable fraction} + \text{endogenous fraction}).\end{aligned}$$

$$\text{Residues} = P_0 + \sum_{n=n_1}^{n_x} (M_n \times A_n) + (\text{Bound residue} \times \text{fraction bioavailable} \times A_b) \dots\dots\dots (1)$$

where

$$\begin{aligned}P_0 &= \text{amount of parent drug per kg of tissue.} \\ n_1..n_x &= \text{different metabolites of the parent drug.} \\ M_n &= \text{amount of (unbound) parent drug metabolite } n \text{ per kg of tissue.} \\ A_n &= \text{toxicological potency of } n \text{ relative to that of parent drug.} \\ A_b &= \text{estimated relative toxicological potency of the metabolites in the bound} \\ &\quad \text{residue (when no information is available, use } A_b = 1)\end{aligned}$$

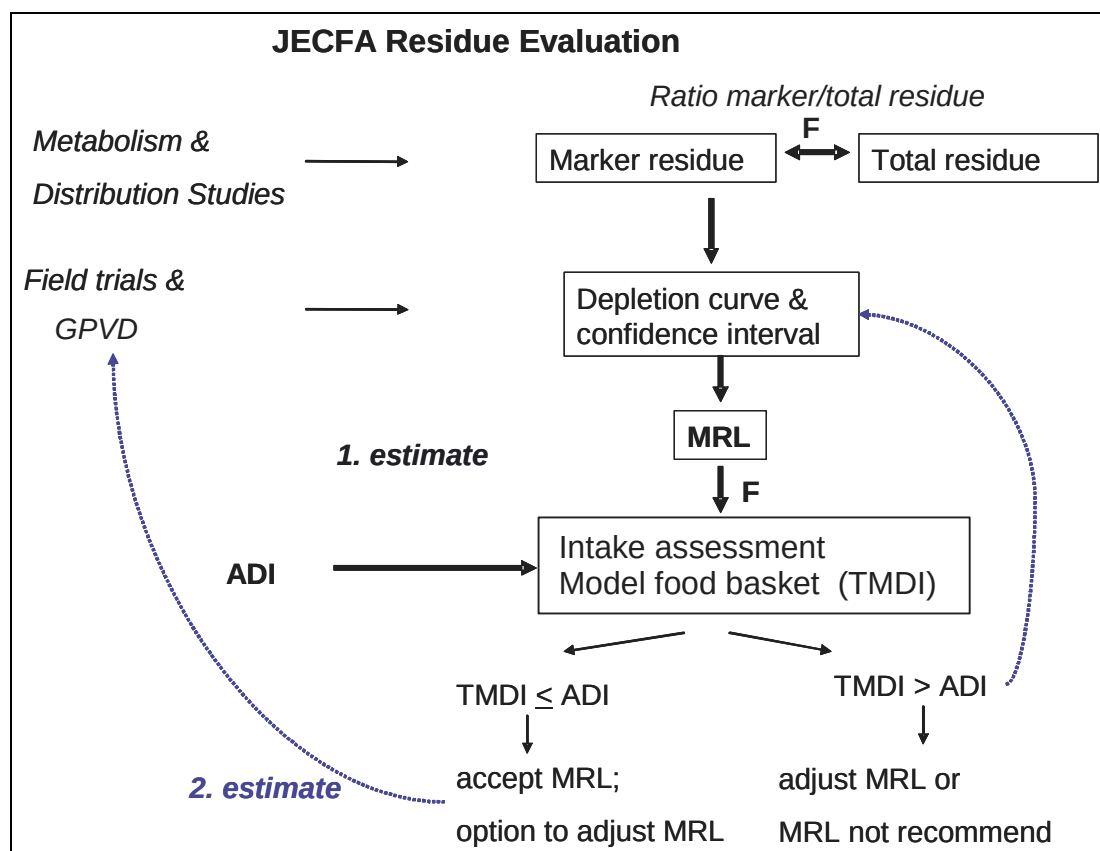
JECFA considers that in the absence of other data, a bound residue should be considered of no greater toxicological concern than the compound for which the ADI was established. In considering the safety of bound residues, JECFA acknowledges that a suitable extractable residue analyte may be selected as a marker compound and used for recommending an MRL if bound residues make up an insignificant portion of the total residue. Where bound residues become a significant portion of the total residues of toxicological significance, then the procedure described may be used to assess their safety. The use of residue data for the purpose of safety assessment is evaluated on a case-by-case basis.

JECFA make final recommendations for MRLs of a veterinary drug in appropriate food animal species and tissues when there are adequate data and compatible with the ADI. Temporary MRLs may be recommended when there is a full ADI yet adequate residue or method performance data are lacking or when the ADI is temporary. The Committee may recommend MRLs "not specified" or "unnecessary" when there is a wide margin of safety of residues when compared with the ADI. Finally, JECFA may determine that MRLs cannot be recommended because of significant deficiencies in either residue data or available analytical methods or when an ADI is not established.

JECFA has devoted a significant effort to analytical methods performance because of the strong role it has in recommending MRLs. JECFA has developed analytical methods performance factors for consideration as suitable for determining compliance with a recommended MRL. Major considerations include accuracy (recovery), precision, reproducibility, sensitivity (dose-response), and selectivity, among others. Use of common laboratory instruments and solvents that do not have environmental or health considerations are important factors. Guidance for analytical method performance factors has been described in individual reports. Methods are considered in cooperation with the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) *ad hoc* Working Group on Methods of Analysis and Sampling.

JECFA has devoted efforts recently to develop statistical tools for data analysis to derive MRLs. A JECFA paper has been prepared as well as a set of proposed statistical tools for JECFA experts to apply for recommending a set of MRLs. The approach has to meet two specific criteria: 1) the time point selected to recommend the MRLs is compatible with registered uses (Good Practice in the Use of Veterinary Drugs), and 2) that it does not result in a theoretical residue exposure in excess of the ADI.

A summary of the JECFA procedures for recommending MRLs is described below.



The MRL recommendation procedure is an iterative process. The MRL is not derived directly from the ADI. If the ADI is based on toxicological end-points, all residues of toxicological relevance are considered, if the ADI is based on microbiological end-points, all residues of microbiological relevance are considered. The MRL recommendation procedure also takes into account the conditions of use (e.g. use of the veterinary drug according to good practice in the use of veterinary drugs GPVD) and the residues that result from such use (e.g. residue depletion studies). It also considers results of radiolabel residue studies, the bioavailability of bound residues, the identification of target tissues and a marker residue, the availability of practical analytical methods, estimated exposure resulting from recommended MRLs and consideration of extension of the MRLs to tissues, eggs and milk of other species.

The initial consideration in recommending an MRL is whether it is sufficiently protective of human health. If the use of the veterinary drug yields an estimated intake of veterinary drug residues consistent with the ADI, the recommended MRLs may then be adjusted accordingly when taking into account the other factors noted above. As a general principle, the Committee will not normally recommend an MRL that results in residue levels that lead to dietary intake exceeding the ADI based on toxicological or microbiological considerations.

11. Please confirm or comment on the following Canadian statement: "it is recognized that JECFA only allocates an ADI for a food additive or veterinary drug under review when JECFA considers that its scientific data base is complete and that there are no outstanding scientific issues". [see para. 68 of Canada Rebuttal Submission]

If there are substantial data gaps and important information missing, JECFA can not establish an ADI. However, JECFA can allocate a temporary ADI when data are sufficient to conclude that use of the

substance is safe over the relatively short period of time required to generate and evaluate further safety data, but are insufficient to conclude that use of the substance is safe over a lifetime. A higher-than-normal safety factor is used when establishing a temporary ADI and an expiration date is established by which time appropriate data to resolve the safety issue should be submitted to JECFA. The temporary ADI is listed in units of mg per kg of body weight. Source: JECFA glossary of terms: <http://www.who.int/ipcs/food/jecfa/glossary.pdf>

12. In paras. 129 and 168 of its Replies to the Panel's questions, the European Communities states that "JECFA's traditional mandate does not allow it to examine all risk management options but restricts it to either propose MRLs or not." Does Codex have risk management options other than (1) the establishment of an MRL, (2) the establishment that an MRL is not necessary, or (3) no recommendation?

JECFA is the risk assessment body and only considers health impact of specific risk management options when specifically requested by CCRVDF, e.g. JECFA could estimate the impact on exposure of different MRLs, if asked to do so. Consideration of risk management options is in the responsibility of the risk management body, hence CCRVDF.

13. With respect to the data used in the evaluation of chemical substances, such as the hormones at issue, what are the data requirements for JECFA's work and how are they determined? Who provides data for such evaluations? Are any records/archives kept by JECFA? Do any confidentiality rules apply to data submitted to JECFA or should all data be publicly available? If confidentiality rules apply, in which circumstances? [see paras. 95-96 of EC Rebuttal Submission (US case), paras. 78-79 of EC Rebuttal Submission (Canada case), para. 123 of Canada Rebuttal Submission]

Data requirements:

In the public call for data for submission to the Joint FAO/WHO JECFA Secretariat that precedes each JECFA meeting, governments, interested organizations, producers of these chemicals, and individuals are invited to submit data relating to the compounds listed in agenda. The data requirements are detailed in the call for data and include the following:

Data relevant to the evaluation of veterinary drug residues in food products of animal origin, including:

1. chemical identity and properties of the drug;
2. its use and dosage range;
3. pharmacokinetic, metabolic, and pharmacodynamic studies in experimental and food-producing animals, and in humans when available;
4. short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity and developmental toxicity studies in experimental animals and genotoxicity studies;
5. special studies designed to investigate specific effects, such as those on mechanisms of toxicity, no-hormonal-effect levels, immune responses, or macromolecular binding;
6. for compounds with antimicrobial activity, studies designed to evaluate the possibility that residues of the compound might have an adverse effect on the microbial ecology of the human intestinal tract; and

7. studies providing relevant data on the use of and exposure to the drug by humans, including studies of effects observed after occupational exposure and epidemiological data following clinical use in humans
8. pharmacokinetic and metabolic studies in experimental animals, target animals, and humans when available (information required by both FAO and WHO);
9. residue-depletion studies with radiolabelled drug in target animals from zero withdrawal time to periods extending beyond the recommended withdrawal time (these studies should provide information on total residues, including free and bound residues, and major residue components to permit selection of a marker residue and target tissue);
10. residue-depletion studies with unlabelled drug for the analysis of marker residue in target animals and in eggs, milk, and honey (these should include studies with appropriate formulations, routes of application, and species, at doses up to the maximum recommended);
11. a description of the analytical procedures used by the sponsor for the detection and determination of parent drug residues with information on validation and performance characteristics; and
12. a review of routine analytical methods that may be used by regulatory authorities for the detection of residues in target tissue, including information on quality assurance systems and sampling procedures recommended.

Additional information can be found in the procedural guidelines for JECFA:

Guidelines for the preparation of toxicological working papers for the Joint FAO/WHO Expert Committee on Food Additives: Residues of veterinary drugs in food, Geneva, August 1996
http://www.who.int/ipcs/food/jecfa/en/guidelines_vet_drugs.pdf and
ftp://ftp.fao.org/es/esn/jecfa/2000-06-30_JECFA_Procedures_MRLVD.pdf

In the particular case of the hormones, JECFA also detailed in the respective report, the additional data needed to perform a complete risk assessment of the individual hormones under review.

Data submissions:

Data are mainly provided by companies who produce the compounds, additional data are sometimes provided by national authorities, such as data on levels analyzed in foods.

Records and archives – confidentiality rules:

The submitted data may be published or unpublished and should contain detailed reports of laboratory studies, including individual animal data. Reference should be made to related published studies, where applicable. Summaries in the form of monographs are helpful, but they are not in themselves sufficient for evaluation. Unpublished confidential studies that are submitted will be safeguarded and will be used only for evaluation purposes by JECFA. Neither FAO nor WHO have facilities for storing printed data for long periods of time, so confidential data will either be returned to the submitter at the submitter's expense or destroyed after the evaluations have been completed. Key material can be stored up to five years and will then be destroyed.

Public accessibility of JECFA assessments:

It is important to note that JECFA evaluations are completely publicly available, and a detailed description of the data evaluated is accessible through the monographs. Specific information regarding the manufacturing process of substances, which are considered confidential for commercial purposes may be excluded from the reports and monographs, if agreed by the Joint FAO/WHO Secretariat.

Short explanation of JECFA publications:

- [WHO Technical Report Series \(TRS\)](#) These reports, published by the World Health Organization, contain concise toxicological evaluations and the chemical and analytical aspects of each substance reviewed by JECFA, as well as information on the intake assessment. Reports reflect the agreed view of the Committee as a whole and describe the basis for their conclusions.
- [WHO Food Additive Series \(FAS\)](#) These monographs, published by the World Health Organization, contain detailed descriptions of the biological and toxicological data considered in the evaluation, as well as the intake assessment, including detailed literature references.
- [Compendium of FAO Veterinary Drug Residue Monographs](#) These monographs, published by the Food and Agriculture Organization, contain the data and the evaluations used to recommend MRLs for veterinary drug residues. They were originally published as the FAO Nutrition Meetings Report Series, and later as FAO Food and Nutrition Papers. The information from these publications has been updated and compiled into FAO Food and Nutrition Paper 41. Individual, fully updated evaluations are also available here in a combined online compendium, searchable by both drug name and functional class. New monographs will be published in the FAO JECFA Monograph series from 2006 onwards.

14. How are experts involved in JECFA's work selected? What are the selection criteria?

Detailed procedures are outlined in the procedural guidelines:

WHO procedural guidelines for JECFA:

http://www.who.int/ipcs/food/jecfa/procedural_guidelines%20_drugs.pdf

FAO procedural guidelines for JECFA:

ftp://ftp.fao.org/es/esn/jecfa/2002-09-24_Vet_Drugs_Proc_Guidelinesb.pdf

Guideline for selection of experts to serve on the roster of JECFA: These guidelines are governed by Procedural rules of FAO and WHO (see response to question 7, first paragraph). Article VI (sections 2, 3 and 7) of the Constitution of FAO and the [Regulations for Expert Advisory Panels and Committees](#) of WHO lay down the basic rules of JECFA. All members and associated drafting experts of JECFA act strictly in their own capacity. Declarations of interest are signed by each expert in advance of the meeting and considered by the Joint FAO/WHO JECFA Secretariat.

JECFA is not a standing committee, the selection of members for each meeting is made after a careful consideration of the scientific credentials of the various candidates, and a balance of scientific expertise and other experience that is considered essential considering the items on the agenda of the meeting. The selection process respects as well FAO and WHO policies on regional representation and gender balance. FAO and WHO meet the costs of experts' attendance at JECFA meetings. Being a joint committee of FAO and WHO, the organizational framework of JECFA complies with the rules of both organizations. The selection process for experts is undertaken in mutual consultation by the Joint Secretariats. When calling for and selecting experts, FAO and WHO assure that selections

complement each other. Both organizations establish listings of experts, called rosters; appointments are for a period of five years. Experts are selected from those rosters for each meeting, in which capacity they either attend the meeting as members or assist the Secretariat with preparatory work before the meeting and usually participate in the meeting itself. Each member invited by WHO must also be a member of a WHO Food Safety Advisory Panel and is appointed by the Director General of WHO. Invitations to each meeting by FAO is decided by the Director General of FAO.

17. Is the table in Exhibit CDA-32 outlining the chronology of JECFA's assessment of the hormones at issue and the resulting documentation complete?

The document describes the published documentation relating to the risk assessment of the individual hormones, reports and monographs, adopted by JECFA and published by WHO and FAO. The list is complete (in some instances page numbers are given only as the first page and in other as the page numbers of entire section in question), with the exception of the summary and conclusions of the 66th JECFA meeting held 20 - 28 February, 2006 (page 3). In this meeting, the Committee further deliberated on the MRLs previously proposed for melengestrol acetate, at the request of CCRVDF (ftp://ftp.fao.org/ag/agn/jecfa/jecfa66_final.pdf).

18. What happens if new evidence or studies throw into doubt a Codex standard? What are the procedures for incorporating more recent developments into Codex work? Has the European Communities approached Codex for this purpose with respect to the hormones at issue in this case?

In general, there is a clear procedure for placing compounds on the agenda of JECFA to perform or update a risk assessment. If new scientific data become available that may impact on an existing risk assessment, there are several possibilities for a compound to be scheduled for re-evaluation by JECFA.

Requests for the evaluation of certain veterinary drugs and consideration of issues of a general nature by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) may come from a number of sources:

1. Codex committees

The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) refers substances to JECFA based on priorities that it establishes using criteria that it has developed that are in accord with accepted procedures of the Codex Alimentarius Commission.

2. FAO and WHO Member States

FAO and WHO Member States may request the inclusion of veterinary drugs on the agenda of JECFA through a direct request to the FAO and WHO Secretariats. Such a request must be accompanied by a commitment to provide the necessary data 6-7 months before the meeting.

3. Sponsors

For veterinary drugs not previously evaluated by JECFA, an industry sponsor may forward a request for evaluation through the government of a Member State to CCRVDF, with a commitment to provide the relevant data. Requests for the re-evaluation of a veterinary drug that has been reviewed by JECFA previously may be forwarded directly to the JECFA Secretariat. As with all other substances on the agenda, the Joint Secretariat includes the substance in the call for data for the meeting to ensure that all interested parties have the opportunity to submit data.

4. JECFA Secretariat

The JECFA secretariat may place a veterinary drug on the agenda for re-evaluation even though no outside request has been received.

5. JECFA itself

The Committee often establishes a temporary ADI or recommends temporary MRLs, with a request for further data by a certain time. These veterinary drugs, which have the highest priority for evaluation, are placed on the agenda of the appropriate meeting by the Joint Secretariat.

Source: WHO procedural guidelines for JECFA, Annex 1:

http://www.who.int/ipcs/food/jecfa/procedural_guidelines%20_drugs.pdf

19. What would be the procedures for requesting JECFA to re-evaluate its recommendations in light of new concerns/evidence? How would an amendment be adopted? Has the European Communities approached JECFA for this purpose with respect to the hormones at issue in this case? [see Exhibit EC-63]

Regarding the procedures for a compound to be re-evaluated please refer to the response under question 18 above.

The re-evaluations of compounds follow the same procedure as an evaluation performed for the first time, with clear identification of the new data that were assessed. Data from previous assessments relevant for the evaluation are also described, and the final assessment published in the report and if relevant also as a monograph addendum. JECFA reports are adopted before the close of the meeting, i.e. the final report for each meeting, including the general considerations as well as the assessments for all compounds on the agenda, are adopted at the meeting before it is adjourned. After that only editorial changes are made.

European Union has not asked the JECFA Secretariat to bring their data referred to in the report of the 11th session of CCRVDF (see below point 1 of question 20) before JECFA for review. The studies referred were finalised later than the 52nd JECFA meeting and the Secretariat has not scheduled these substances on the agenda of JECFA since that meeting.

20. What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999? Were the residues data used for the three natural hormones in 1999 the same as those used in 1988? What additional information was used for the JECFA evaluation in 1999 of the three natural hormones which was not available in 1988? How did the conclusions differ? What led JECFA to establish ADIs for the three natural hormones? What are the implications of establishing ADIs? Why were JECFA's more recent recommendations not considered by CCRVDF? What is the status of these recommendations? [see paras. 96-97 of EC Rebuttal Submission (US case), paras. 79-80 of EC Rebuttal Submission (Canada case)]

(1) What were the reasons for the re-evaluation by JECFA of the three natural hormones in 1999?

The natural hormones were placed on the agenda for re-evaluation by the JECFA secretariat, as documented in the report of the 11th Session of CCRVDF:

From the report of the 11th Session of CCRVDF, ALINORM99/31:

125. The question was raised as to why the natural hormones (estradiol-17b, progesterone, and testosterone) had been placed on the agenda of the JECFA for reevaluation. It was pointed out that they were placed on the agenda at the initiative of the JECFA Secretariat to ensure that all the latest information had been evaluated. On the evaluation of natural hormones, the European Commission pointed out that it had written to the JECFA Secretariat in order to make JECFA aware that a number of substantial studies were currently being prepared by the EU and had requested that the JECFA evaluation be deferred to a later JECFA meeting. The European Community therefore reiterated the request to defer the JECFA consideration.

ALINORM 99/31 APPENDIX VIII

PRIORITY LIST OF VETERINARY DRUGS REQUIRING EVALUATION OR REEVALUATION

1. Substances scheduled for evaluation or reevaluation at the fifty-second meeting of JECFA in February 1999:

Substances on the previous priority list of CCRVDF	Substances recommended for reevaluation by JECFA (temporary ADI and/or MRLs) or by the JECFA Secretariat
Deltamethrin (residues) – toxicological evaluation by 2000 JMPR Permethrin (residues) – toxicological evaluation by 1999 JMPR Phoxim Porcine somatotropin Carazolol	Abamectin (residues; referral from JMPR) Azaperone (analytical method) Dihydrostreptomycin/streptomycin (residues) Doramectin (residues) Natural hormones (estradiol-17 β , progesterone, and testosterone) Thiamphenicol

JECFA can decide to reevaluate previous assessment when the Committee is made aware that there is new data which may be pertinent to the risk assessment of the substances in question. The European Union had claimed in the 1997 WTO hormone dispute that new evidence showed that oestradiol-17 β is a directly acting genotoxic carcinogen. Also for the other substances a substantial amount of new studies had been published since the 32nd meeting. Also the 32nd Meeting produced no toxicological monograph for the three nature-identical hormones. The toxicological/endocrinological/epidemiological data for the 52nd Meeting were retrieved by means of an exhaustive literature survey.

- (2) **Were the residues data used for the three natural hormones in 1999 the same as those used in 1988?**

In the 1988 evaluation, the data has been described in FAO Food and Nutrition Paper 41/1 (1988). In the 1999 evaluation, new information for the three natural hormones was provided, including the complete dossier submitted to the US Food and Drug Administration. FDA kindly permitted the FAO expert to the Committee to search all their relevant files for data. A more complete and transparent assessment of all data, including statistical evaluation, was made (FAO Food and Nutrition Paper 42/12, 2000, p. 37-90). Most of the studies were the same. However, a few additional investigational studies were also reviewed. JECFA also performed a more detailed thorough review of the validity of the analytical methods used in the studies and used only data generated using valid methods. It also performed more detailed statistical and graphical analyses of the data. Since the FAO FNP 41/12

monograph provides all raw data used (in graphical form) and all the calculations performed, the document is also more transparent than the corresponding monograph produced by the 32nd Meeting.

(3) What additional information was used for the JECFA evaluation in 1999 of the three natural hormones which was not available in 1988?

From the report of the 52nd JECFA meeting, TRS 893:

Estradiol-17 β , progesterone and testosterone were re-evaluated at the present meeting to take into consideration any data that had been generated since their previous review and to make a quantitative estimate of the amounts that could be consumed safely.

Toxicological data

Estradiol-17 β . The Committee considered published data from studies on the oral bioavailability, metabolism, short-term toxicity, reproductive toxicity, genotoxicity and long-term toxicity/carcinogenicity of exogenous estrogens. Numerous reports on studies of the use of exogenous estrogens in women were considered, as were studies in experimental animals on the mechanism of action of estradiol-17 β . The extensive database derived from the results of epidemiological studies in women taking oral contraceptive preparations containing estrogens or postmenopausal estrogen replacement therapy was also used to evaluate the safety of estradiol-17 β .

Progesterone. The Committee considered published data from studies on the oral bioavailability, metabolism, short-term toxicity, reproductive toxicity, genotoxicity and long-term toxicity/carcinogenicity of progesterone. Numerous reports of studies on progesterone in humans were considered. In addition, the extensive database derived from women taking progesterone as a component of oral contraception, as injectable progestogen-only contraception, and in postmenopausal hormone replacement therapy was used to support the safety evaluation.

Testosterone. The Committee considered published data from studies on the oral bioavailability, metabolism, short-term toxicity, reproductive toxicity, genotoxicity and long-term toxicity/carcinogenicity of testosterone. Reports of studies on testosterone in humans were also considered.

Residue studies for the three hormones. Please see answer to point 2 above.

(4) How did the conclusions differ?

Estradiol-17 β

Estradiol was reviewed previously by the Committee, at its thirty-second meeting (1988), when it concluded that the establishment of an acceptable residue level and an ADI was 'unnecessary', based on the conclusion that this is a hormone that is produced endogenously in human beings and shows great variation in level according to age and sex. This conclusion was based on studies of the patterns of use of estradiol for growth promotion in cattle, the residues in animals, analytical methods, toxicological data from studies in laboratory animals, and clinical findings in human subjects. The Committee further concluded that estradiol residues resulting from its use for growth promotion in accordance with good husbandry practices were unlikely to be a hazard to humans.

On the basis of its safety assessment of residues of estradiol-17 β , and in the view of the difficulty of determining the levels of residues attributable to the use of this hormone as a growth promoter in cattle, the Committee concluded that it was unnecessary to establish an Acceptable Residue Level.

At its 52nd meeting in 1999, estradiol-17 β was re-evaluated to take into consideration any data that had been generated since the previous review and to make a quantitative estimate of the amount that could be consumed safely. The Committee established an ADI of 0-50 ng/kg bw on the basis of the NOEL of 0.3 mg/day (equivalent to 5 μ g/kg bw per day) in studies of changes in several hormone-dependent parameters in postmenopausal women. A safety factor of 10 was used to account for normal variation among individuals, and an additional factor of 10 was added to protect sensitive populations.

Progesterone

Progesterone was reviewed previously by the Committee, at its thirty-second meeting (1988). The Committee then concluded, that the amount of exogenous progesterone ingested from meat of treated animals would not be capable of exerting hormonal a effect, and therefore any toxic effect, in human beings. The Committee deemed it 'unnecessary' to set an ADI for a hormone that is produced endogenously in human beings and shows marked physiological variation in levels according to age and sex. The Committee concluded that residues arising from the use of progesterone as a growth promoter in accordance with good animal husbandry practice are unlikely to pose a hazard to human health.

On the basis of its safety assessment of residues of progesterone, and in the view of the difficulty of determining the levels of residues attributable to the use of this hormone as a growth promoter in cattle, the Committee concluded that it was unnecessary to establish an Acceptable Residue Level.

At its 52nd meeting in 1999, progesterone was re-evaluated to take into consideration any data that had been generated since the previous review and to make a quantitative estimate of the amount that could be consumed safely. The Committee established an ADI of 0-30 μ g/kg bw for progesterone on the basis of the LOEL of 200 mg/day (equivalent to 3.3 mg/kg bw) for changes in the uterus. A safety factor of 100 was used to allow for extrapolation from a LOEL to a NOEL and to account for normal variation among individuals.

Testosterone

Testosterone was reviewed previously by the Committee, at its thirty-second meeting (1988). The Committee the considered an ADI 'unnecessary' for a hormone that is produced endogenously in human beings and shows marked physiological variation in levels according to sex and age. The Committee concluded that residues resulting from the use of testosterone as a growth promoter in accordance with good animal husbandry practice are unlikely to pose a hazard to human health.

On the basis of its safety assessment of residues of testosterone, and in the view of the difficulty of determining the levels of residues attributable to the use of this hormone as a growth promoter in cattle, the Committee concluded that it was unnecessary to establish an Acceptable Residue Level.

At its 52nd meeting in 1999, testosterone was re-evaluated to take into consideration any data that had been generated since the previous review and to make a quantitative estimate of the amount that could be consumed safely. The Committee established an ADI of 0-2 μ g/kg bw for testosterone on the basis of the NOEL of 100 mg/day (equivalent to 1.7 mg/kg bw per day) in the study of eunuchs and a safety factor of 1000. The large safety factor was used in order to protect sensitive populations and because of the small number of subjects in the study from which the NOEL was identified.

Conclusions in residues evaluation of all three hormones

The conclusions concerning residues were equivalent in the 1988 evaluation and the 1999 evaluation, but were based on a more detailed discussion. The 52nd JECFA performed a detailed theoretical intake assessment based on a worst case scenario (all animals are slaughtered at the time of the highest hormone levels - this time point differs largely from the time point at which the benefit due to the anabolic effect is greatest). In this assessment intake estimates for preferential meat eaters were performed on the basis of the hormone levels of treated animals in comparison with the corresponding levels in untreated animals and the additional "burden" or "excess intake" was calculated.

For total estrogens the highest excess intakes from approved uses calculated this way were in the order of magnitude of 30-50 ng/person/day. This range of intake is less than 2% of the ADI for estradiol-17 β established by JECFA at the 52nd meeting. For certain experimental studies carried out with experimental combinations resulted in an excess intake of around 4% of the ADI.

The highest excess intake of progesterone, the only relevant hormonal active residue from treatment with progesterone, was below 500 ng/person/day for the approved uses of this hormone. This corresponds to 0.003% of the ADI for progesterone established by JECFA.

For testosterone, the highest intake of the free hormone was approximately 60 ng/person/day for all approved uses of this hormone. This represents around 0.2% of the ADI for testosterone established by JECFA.

JECFA also noted that hormone concentrations found in individual populations of treated animals, although they were typically statistically significant higher than untreated controls, were well within the physiological range of these substances in bovine animals. The data assessed and the worst case scenario calculations made indicated a wide margin of safety of consumption of residues from animals treated in accordance with good practice of use of the veterinary drugs containing the hormones in question. JECFA therefore concluded that there was no need to specify numerical maximum residue levels for the three hormones and recommended MRLs not specified in bovine tissues.

(5) What led JECFA to establish ADIs for the three natural hormones?

The additional data reviewed and the need to establish an ADI as quantitative estimate for a safe oral intake. The exposure assessment performed would then allow the comparison of the estimated intake with the ADI. This can mean that maximum residue limits are recommended or if the margin of safety is wide that there is no necessity to derive numerical values.

(6) What are the implications of establishing ADIs?

An ADI is an estimate of a quantity of a substance that can be consumed over life-time without any appreciable health risk, i.e. it is a measure for a safe chronic intake level. The ADI can be used to estimate the safety of proposed maximum residue levels in food and the resulting intake estimates. The ADI can then be compared to actual or estimated intake levels, which are calculated from actual or estimated occurrence data in food times the amount of food consumed. This then leads to conclusions on the safety of the food supply, or of specific foods, including tissues of animal origin. JECFA uses a standard food basket for foods of animal origin, which includes 500 g of meat to be eaten every day of life.

Sufficient new data from observations in humans were available to the 52nd JECFA which were suitable to derive ADIs. The ADI not only provides an estimate of daily intakes which can be

accepted over life time without appreciable health risks, it also enables a quantitative comparison of the excess intakes calculated on the basis of the above mentioned worst case scenario (see point 4 above). The Committee found that the excess intake was in the order of only 0.02 to 4% of the ADI depending on the substance and the product used for the treatment of the animals.

Moreover, the establishment of an ADI implies that there is a threshold of effect for such a compound, below which no toxicological effects occur.

(7) Why were JECFA's more recent recommendations not considered by CCRVDF?

From 12th CCRVDF report, ALINORM 01/31

under report from JECFA: MRLs for estradiol-17 β , progesterone and testosterone were recommended as "not specified".

Under MRLs:

Estradiol-17 β , Progesterone and Testosterone

84. Recognizing that this Committee had not requested the re-evaluation of these substances and that the new MRLs recommended by the 52nd JECFA did not differ significantly from the current MRLs, the Committee **decided** not to consider these new recommendations. The MRLs not specified adopted by Codex were the same as those recommended by JECFA at the 52nd meeting.

ANNEX 1



**Food and Agriculture Organization
of the United Nations**



**World Health
Organization**

FACT SHEET - WHAT IS JECFA? (9 February 2006)

Introduction

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). It has been meeting since 1956, initially to evaluate the safety of food additives. Its work now also includes the evaluation of contaminants, naturally occurring toxicants and residues of veterinary drugs in food.

To date, JECFA has evaluated more than 1500 food additives, approximately 40 contaminants and naturally occurring toxicants, and residues of approximately 90 veterinary drugs. The Committee has also developed principles for the safety assessment of chemicals in food that are consistent with current thinking on risk assessment and take account of recent developments in toxicology and other relevant scientific areas such as microbiology, biotechnology, exposure assessment, food chemistry including analytical chemistry and assessment of maximum residue limits for veterinary drugs.

JECFA normally meets twice a year with individual agendas covering either (i) food additives, contaminants and naturally occurring toxicants in food or (ii) residues of veterinary drugs in food. The membership of the meetings varies accordingly, with different sets of experts being called on depending on the subject matter.

History and Background

The evaluation of food additives at the international level was initiated as a result of a Joint FAO/WHO Conference on Food Additives held in Geneva, Switzerland in 1955. The Conference recommended to the Directors-General of FAO and WHO that one or more expert committees should be convened to address the technical and administrative aspects of chemical additives and their safety in food. This recommendation provided the basis for the first meeting of JECFA. As of January 2006 the committee has met 65 times and the 67th meeting in June 2006 marks the 50th anniversary of JECFA.

Purpose

JECFA serves as an independent scientific committee which performs risk assessments and provides advice to FAO, WHO and the member countries of both organizations. The requests for scientific advice are for the main part channelled through the Codex Alimentarius Commission (CAC) in their work to develop international food standards and guidelines under the Joint FAO/WHO Food

Standards Programme. The main purposes of this Programme are protecting health of the consumers and ensuring fair trade practices in the food trade. The advice to CAC on food additives, contaminants and naturally occurring toxicants is normally provided to the Codex Committee on Food Additives and Contaminants (CCFAC) and advice on residues of veterinary drugs to the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF).

All countries need to have access to reliable risk assessment of chemicals in food, but not all have the expertise and funds available to carry out separate risk assessments on large numbers of chemicals. JECFA performs a vital role in providing a reliable and independent source of expert advice in the international setting, thus contributing to the setting of standards on a global scale for the health protection of consumers of food and for ensuring fair practices in the trade in safe food. Some countries use information from JECFA in the establishment of national food safety control programmes and CCFAC and CCRVDF develop standards based on evaluations by JECFA.

Under the terms of the Sanitary and Phytosanitary agreement (SPS), scientific, risk based standards established by CAC should be employed in international trade of food. Therefore, governments are likely to request advice from Codex committees, and consequently from JECFA and other international scientific bodies, on the implementation of national standards and legislation related to food safety.

Membership of the Committee

FAO and WHO have complementary functions in selecting experts to serve on the Committee. FAO is responsible for selecting members with chemical expertise for the development of specifications for the identity and purity of food additives, for the assessment of residue levels of veterinary drugs in food, and to assess the quality of the monitoring data. WHO is responsible for selecting members for the toxicological evaluations of the substances under consideration, in order to establish acceptable daily intakes (ADIs), or other relevant guidance values, or to give a quantitative estimate of the health risk. Both FAO and WHO invite members who are responsible for assessing exposure. Both organizations establish listings of experts, called *rosters*; appointments are for a period of five years. Experts are selected from those rosters for each meeting, in which capacity they either attend the meeting as members or assist the Secretariat with preparatory work before the meeting and usually participate in the meeting itself. The selection of members for each meeting is made after a careful consideration of the scientific credentials of the various candidates, and a balance of scientific expertise and other experience that is considered essential considering the items on the agenda of the meeting. FAO and WHO meet the costs of experts' attendance at JECFA meetings.

Being a joint committee of FAO and WHO, the organizational framework of JECFA complies with the rules of both organizations. The selection process for experts is undertaken in mutual consultation by the Joint Secretariats. When calling for and selecting experts, FAO and WHO assure that selections complement each other. The selection process respects as well FAO and WHO policies on regional representation and gender balance.

Terms of Reference of the Committee

For food additives, including enzymes and flavouring agents, contaminants and naturally occurring toxicants, the Committee

- (i) elaborates principles for evaluating their safety and for quantifying their risks;
- (ii) conducts toxicological evaluations and establishes acceptable daily intakes (ADIs) or tolerable intakes for chronic exposure and other guidance values for acute exposure;

- (iii) assess the performance, quality and applicability of analytical methods;
- (iv) prepares specifications of purity for food additives; and
- (v) assesses exposure of populations to chemical substances in food.

For residues of veterinary drugs in food, the Committee

- (i) elaborates principles for evaluating their safety and for quantifying their risks;
- (ii) establishes ADIs and other guidance values for acute exposure
- (iii) recommends maximum residue limits (MRLs) for target tissues; and
- (iv) determines appropriate criteria for and evaluates methods of analysis for detecting and/or quantifying residues in food.

Risk assessment

For food additives and veterinary drug residues, JECFA normally establishes ADIs on the basis of available toxicological data and other information. Specifications for the identity and purity of food additives are also developed, which help to ensure that the commercial product is of appropriate quality, can be manufactured consistently, and is equivalent to the material that was subjected to the toxicological testing.

For contaminants and naturally occurring toxicants, levels corresponding to 'tolerable' intakes such as the provisional maximum tolerable daily intake (PMTDI) or the provisional tolerable weekly intake (PTWI) are normally established when there is an identifiable no-observed-effect level. When a no-observed-effect level cannot be identified, the Committee aims to provide other advice depending on the circumstances and the data available.

For veterinary drug residues, maximum residue limits (MRLs) in target animal tissues, milk and eggs are developed taking into account Good Practice in the use of Veterinary Drugs. The application of these MRLs provides assurance that when the drug has been used properly, the intake of residues from animal produce is unlikely to exceed the ADI.

JECFA experts are expected to conduct extensive literature searches on the substances for consideration by the committee, in addition to the review of information submitted by sponsors and national governments.

JECFA also develops general principles and methods for the risk assessment of chemicals in food. To keep abreast in the variety of scientific disciplines necessary for the conduct of up-to-date risk assessments, continuous review and update of the evaluation processes are necessary. Moreover, JECFA plays an important role in the international harmonization of risk assessments of chemicals in food.

Reports and publications

An electronic summary with the main findings and conclusions of the meeting is published by the Joint Secretariat shortly after each meeting. Usually, the information is mainly in tabular format, including the details of ADIs and MRLs recommended. This is available on the website of JECFA at FAO and WHO.

The concise description of the key data used in the assessments, the evaluation of these data and the conclusions of the committee are published by WHO in the Technical Report Series. These reflect the view of the committee as a whole, albeit in rare events where one or more members cannot agree to the conclusions, the positions of the dissenting expert(s) and the reason for the disagreement will be recorded in the report.

Toxicological and exposure assessment monographs are published in the WHO Food Additive Series (FAS). These monographs contain the detailed description and evaluation of all the biological and toxicological data considered in the evaluation and provide references to the cited literature. A detailed exposure assessment is also included in the monographs.

The reports and toxicological monographs are available from the WHO JECFA website <http://www.who.int/ipcs/publications/jecfa/en/>.

Specifications monographs on the identity and purity of food additives developed at meetings and agreed on have been published in the Compendium of Food Additive Specifications (Food and Nutrition Paper 52) and are available from the FAO JECFA website <http://www.fao.org/ag/agn/jecfa/database/cover.htm>. A new Combined Compendium replaces the earlier edition and incorporates all the additions and revisions made since 1992, up to and including those contained in FNP 52 Addendum 13. It is being published as the first document under a new publication series, the FAO JECFA Monographs as Volume 1 - 3. Volume 4 of this first Monograph series will provide a reference for analytical methods and test procedures used in and referenced by the specifications and which replaces the previous Food and Nutrition Paper 5.

Monographs on veterinary drug residues, which summarize the data and the evaluations used for the recommendation of MRLs, have been published in the Food and Nutrition Paper Series 41 and are available from the FAO JECFA website http://www.fao.org/ag/agn/jecfa/jecfa_vetdrug_en.jsp. New monographs will be published in the FAO JECFA Monograph series from 2006 onwards.

Information on the activities and output from JECFA meetings are available at the dedicated JECFA websites at FAO http://www.fao.org/ag/agn/jecfa/index_en.stm and WHO <http://www.who.int/ipcs/food/jecfa/en/>.

ANNEX E-3

REPLIES OF THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER TO CERTAIN QUESTIONS POSED BY THE PANEL TO INTERNATIONAL ORGANIZATIONS

21. What is the mandate of the International Agency for Research on Cancer?

According to the statute of the International Agency for Research on Cancer, "The objective of the International Agency for Research on Cancer shall be to promote international collaboration in cancer research. The Agency shall serve as a means through which Participating States and the World Health Organization, in liaison with the International Union against Cancer and other interested international organizations, may cooperate in the stimulation and support of all phases of research related to the problem of cancer." One of the Agency's functions is "the collection and dissemination of information on epidemiology of cancer, on cancer research and on the causation and prevention of cancer throughout the world."

22. Who are the members of the IARC?

According to the statute of the International Agency for Research on Cancer, "The Agency shall comprise: (a) the Governing Council; (b) the Scientific Council; (c) the Secretariat." The Governing Council shall be composed of one representative of each Participating State and the Director-General of the World Health Organization. In June 2006, the Participating States of the Agency are Australia, Belgium, Canada, Denmark, Finland, France, Germany, India, Italy, Japan, Norway, the Netherlands, the Republic of Korea, Spain, Sweden, Switzerland, the United Kingdom, and the United States. The Scientific Council is composed of a maximum of twenty highly qualified scientists, selected on the basis of their technical competence in cancer research and allied fields. The Secretariat consists of the Director of the Agency and such technical and administrative staff as may be required.

23. What are IARC Monographs? How are they prepared?

The *IARC Monographs* are a series of scientific reviews that identify environmental factors that can increase the risk of human cancer.

IARC convenes an international, interdisciplinary Working Group of expert scientists to develop each volume of *IARC Monographs*. The Working Group writes a critical review of the pertinent scientific literature and an evaluation of each agent's potential to cause cancer in humans.

IARC Monographs are developed during an 8-day meeting whose objectives are peer review and consensus. Before the meeting, the Working Group searches the scientific literature and writes preliminary working papers for the critical review. At the meeting, four subgroups (exposure, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review these working papers and develop consensus subgroup drafts. Then the Working Group meets in plenary session to review the subgroup drafts and develop a consensus evaluation. After the meeting, IARC scientists review the final draft for accuracy and clarity before publication.

The evaluation is developed in steps. The subgroup of epidemiologists proposes an evaluation of the evidence of cancer in humans as *sufficient evidence*, *limited evidence*, *inadequate evidence*, or *evidence suggesting lack of carcinogenicity*. A subgroup of toxicologists and pathologists proposes an evaluation of the evidence of cancer in experimental animals, choosing one of the same descriptors. Combination of these two partial evaluations yields a preliminary default evaluation that the agent is either:

- *Carcinogenic to humans (Group 1)*
- *Probably carcinogenic to humans (Group 2A)*
- *Possibly carcinogenic to humans (Group 2B)*
- *Not classifiable as to its carcinogenicity to humans (Group 3)*
- *Probably not carcinogenic to humans (Group 4)*

When the epidemiological evidence is *sufficient*, the final evaluation is *carcinogenic to humans*, regardless of the experimental evidence. In other cases, the mechanistic and other relevant data are considered to determine whether the default evaluation should be modified, upwards or downwards. A subgroup of experts in cancer mechanisms assesses the strength of the mechanistic data and whether the mechanisms of tumour formation in experimental animals can operate in humans. The overall evaluation is a matter of scientific judgement, reflecting the combined weight of the evidence.

Working Groups are selected on the basis of (1) knowledge and experience and (2) absence of real or apparent conflicts of interests. Consideration is given also to demographic diversity and balance of scientific findings and views. Each potential participant completes the World Health Organization's Declaration of Interests, which IARC assesses to determine whether there is a conflict that warrants some limitation on participation. An expert with a real or apparent conflict of interests may not draft text that describes or interprets cancer data, participate in the evaluations, or serve as chair. IARC strives to ensure that the Working Group is free from all attempts at interference, before and during the meeting. This includes lobbying, written materials, and meals or other favours offered by interested parties. Working Group Members are asked not to discuss the subject matter with anyone outside the meeting and to report all attempts at interference.

24. Please briefly explain the groupings that are used to categorize "potentially carcinogenic agents"? What are the implications when an "agent" is placed in one of the IARC categories?

IARC uses the following groupings to characterize potentially carcinogenic agents:

Carcinogenic to humans (Group 1). This category is used when there is *sufficient evidence of carcinogenicity* in humans.

Probably carcinogenic to humans (Group 2A). This category is generally used when there is *limited evidence* in humans and *sufficient evidence* in experimental animals.

Possibly carcinogenic to humans (Group 2B). This category is generally used when there is *limited evidence* in humans or *sufficient evidence* in experimental animals, but not both.

Not classifiable as to its carcinogenicity to humans (Group 3). This category is generally used when there is *inadequate evidence* in humans and *inadequate* or *limited evidence* in experimental animals. Agents that do not fall into any other group are also placed in this category.

Probably not carcinogenic to humans (Group 4). This category is generally used when there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals.

Mechanistic and other relevant data also contribute to the grouping. Further details can be found in the Preamble to the *IARC Monographs* (<http://monographs.iarc.fr>).

25. Which of the six hormones at issue in this dispute (oestradiol-17 β , progesterone, testosterone, trenbolone acetate, zeranol, and melengestrol acetate) have been evaluated by the IARC? Have any specific risks from the consumption of meat from cattle treated with these growth promotion hormones been assessed by the IARC?

IARC has evaluated steroidal estrogens as *carcinogenic to humans* (Group 1); for oestradiol-17 β there is *sufficient evidence of carcinogenicity* in experimental animals (Volume 21, 1979; Supplement 7, 1987; Volume 72, 1999).

IARC has evaluated progestins as *possibly carcinogenic to humans* (Group 2B), based on *sufficient evidence of carcinogenicity* in experimental animals (Volume 21, 1979; Supplement 7, 1987).

For testosterone, IARC has determined that there is *sufficient evidence of carcinogenicity* in experimental animals and advised, "In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard testosterone as if it presented a carcinogenic risk to humans" (Volume 21, 1979).

Trenbolone acetate, zeranol, and melengestrol acetate have not been evaluated by IARC, nor have the specific risks from the consumption of meat from cattle treated with these growth promotion hormones.

26. How does the work of the IARC feed into the work of national regulatory agencies or international bodies, in particular with respect to assessments of risks from the consumption of meat from cattle treated with the six growth promoting hormones at issue in this dispute?

The *IARC Monographs* are used by national and international health agencies as a source of information on potential carcinogens and as scientific support for their actions to prevent exposure to potential carcinogens. The *Monographs* are used by such national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes, and decide among alternative options for public health decisions.
