



**Food and Agriculture Organization  
of the United Nations**



**World Health  
Organization**

**JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES  
Seventieth meeting (Residues of veterinary drugs)  
Geneva, 21–29 October 2008**

**SUMMARY AND CONCLUSIONS**

*Issued 7 November 2008*

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Geneva, Switzerland, from 21 to 29 October 2008. The purpose of the meeting was to evaluate residues of certain veterinary drugs in food.

Dr J.G. McLean, Camberwell, Victoria, Australia, served as Chairman, and Dr G. Swan, Onderstepoort, South Africa, served as Vice-Chairman.

Dr A. Wennberg, Nutrition and Consumer Protection Division, Food and Agriculture Organization of the United Nations, and Dr A. Tritscher, Department of Food Safety, Zoonoses and Foodborne Diseases, World Health Organization, served as Joint Secretaries.

The present meeting was the seventieth in a series of similar meetings and was the eighteenth meeting of JECFA convened to consider residues of veterinary drugs in food. The tasks before the Committee were to further elaborate principles for evaluating the safety of residues of veterinary drugs in food and for establishing acceptable daily intakes (ADIs) and recommend maximum residue limits (MRLs) for certain drugs when they are administered to food-producing animals in accordance with good practice in the use of veterinary drugs.

The report of the meeting will appear in the WHO Technical Report Series. Its presentation will be similar to that of previous reports, namely, general considerations, comments on specific substances, and recommendations. The report will include an annex containing a detailed table (similar to Annex 1 in this summary) summarizing the conclusions reached by the Committee relating to ADIs and MRLs.

Items of a general nature that contain information that the Committee would like to disseminate quickly are included in Annex 2. The participants are listed in Annex 3.

Toxicological monographs summarizing the data that were considered by the Committee in establishing ADIs will be published in *WHO Food Additives Series No. 61*. Residue monographs summarizing the data that were considered by the Committee in recommending MRLs will be published in *FAO JECFA Monographs No. 6*.

More information on the work of JECFA is available at

[www.fao.org/ag/agn/jecfa/index\\_en.stm](http://www.fao.org/ag/agn/jecfa/index_en.stm) and [www.who.int/pcs/jecfa/jecfa.htm](http://www.who.int/pcs/jecfa/jecfa.htm)

*The issuance of this document does not constitute formal publication. The document may, however, be freely reviewed, abstracted, reproduced, or translated, in whole or in part, but not for sale or use in conjunction with commercial purposes.*

**Annex 1****Recommendations on the substances on the agenda****Avilamycin** (antimicrobial agent)

Acceptable daily intake: The Committee established an ADI of 0–2 mg/kg body weight on the basis of a NOAEL of 150 mg avilamycin activity/kg body weight per day and a safety factor of 100 and rounding to one significant figure.

Residue definition: Dichloroisoevernic acid (DIA).

**Recommended maximum residue limits (MRLs)**

Species	Skin/fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Pigs	200	200	300	200
Chicken	200	200	300	200
Turkey	200	200	300	200
Rabbits	200	200	300	200

**Dexamethasone** (Glucocorticosteroid)

Acceptable daily intake: The Committee established an ADI of 0–0.015 µg/kg body weight at the 42nd meeting of the Committee (WHO TRS No. 851, 1995).

Residue definition: Dexamethasone.

**Recommended maximum residue limits (MRLs)**

Species	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)	Milk (µg/l)
Cattle	1.0	2.0	1.0	0.3
Pigs	1.0	2.0	1.0	
Horses	1.0	2.0	1.0	

**Malachite green** (antimicrobial agent and contaminant)

Acceptable daily intake: The Committee considered it inappropriate to establish an ADI for malachite green and did not support the use of malachite green for food-producing animals.

Residues: The Committee did not recommend MRLs for malachite green and leucomalachite green, as it did not support the use of malachite green for food-producing animals.

**Melengestrol acetate** (production aid)

Acceptable daily intake: The Committee established an ADI of 0–0.03 µg/kg body weight at its 54th meeting (WHO TRS No. 900, 2001). It did not consider it necessary to reconsider the ADI at the current meeting on the basis of new data provided.

Residues: The MRLs that were recommended by the 66th meeting of the Committee (WHO TRS No. 939, 2006) were not reconsidered and were maintained.

**Monensin** (antimicrobial agent and production aid)

Acceptable daily intake: The Committee established an ADI of 0–10 µg/kg body weight on the basis of a NOAEL of 1.14 mg/kg body weight per day and a safety factor of 100 and rounding to one significant figure.

Residue definition: Monensin

**Recommended maximum residue limits (MRLs)**

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)	Milk (µg/kg)
Cattle	100	10	10	10	2
Sheep	100	10	10	10	
Goats	100	10	10	10	
Chicken	100	10	10	10	
Turkey	100	10	10	10	
Quail	100	10	10	10	

**Narasin** (antimicrobial agent and production aid).

Acceptable daily intake: The Committee established an ADI of 0–5 µg/kg body weight on the basis of a NOAEL of 0.5 mg/kg body weight per day and a safety factor of 100.

Residues: Narasin A

**Recommended maximum residue limits (MRLs)**

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Cattle	50 <sup>a</sup>	15 <sup>a</sup>	50 <sup>a</sup>	15 <sup>a</sup>
Chicken	50	15	50	15
Pigs	50	15	50	15

<sup>a</sup> The MRL is temporary. Before re-evaluation of narasin with the aim of recommending MRLs in tissues of cattle, the Committee would require a detailed description of a regulatory method, including its performance characteristics and validation data. This information is required by the end of 2010.

**Tilmicosin** (antimicrobial agent)

Acceptable daily intake: The Committee established an ADI of 0–40 µg/kg body weight at its 47th meeting (WHO TRS No. 876, 1998).

Residue definition: Tilmicosin.

**Recommended maximum residue limits (MRLs)**

Species	Skin/fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Chicken	250	600	2400	150
Turkey	250	1200	1400	100

The Committee was not able to recommend a MRL for sheep milk.

Before a re-evaluation of tilmicosin with the aim of recommending MRLs in tissues of rabbits, the Committee would require adequately designed residue studies with doses and routes of administration under authorized conditions of use and using a validated method suitable for the purpose.

**Triclabendazole** (anthelmintic)

Acceptable daily intake: The Committee established an ADI of 0–3µg/kg body weight at its 40th meeting (WHO TRS No. 832, 1993)

Residue definition: Ketotriclabendazole

**Recommended maximum residue limits (MRLs)**

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)
Cattle	100	400	850	250
Sheep	100	200	300	200

**Tylosin** (antimicrobial agent)

Acceptable daily intake: The Committee established an ADI of 0–30 µg/kg body weight based on a microbiological end-point derived from in vitro MIC susceptibility testing and faecal binding data ( $MIC_{calc} = 1.698$ ).

Residue definition: Tylosin A

**Recommended maximum residue limits (MRLs)**

Species	Fat (µg/kg)	Kidney (µg/kg)	Liver (µg/kg)	Muscle (µg/kg)	Skin/fat (µg/kg)	Milk (µg/kg)	Eggs (µg/kg)
Cattle	100	100	100	100		100	
Pigs	100	100	100	100			
Chicken		100	100	100	100		300

## Annex 2

### General considerations

*An edited version of this section will appear in the report of the seventieth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). It is reproduced here so that the information can be disseminated quickly. This draft will be subject to extensive editing.*

#### **2.1 A hypothesis driven decision tree approach for the safety evaluation of residues of veterinary drugs**

In response to recommendations of the sixty-sixth JECFA (WHO TRS No. 939, 2006), a small working group developed a concept paper entitled “A Hypothesis-Driven Decision Tree Approach for the Safety Evaluation of Residues of Veterinary Drugs” for discussion at the current meeting. The concept paper offers a hypothesis-driven decision tree approach to the risk assessment of residues of veterinary drugs that builds upon the foundation in risk analysis to provide greater flexibility in the advice that JECFA can provide on issues relating to the potential human health effects of residues of veterinary drugs. In particular, it offers possible strategies for assessing compounds for which there are few, if any, sponsors, for which the database is old and/or incomplete, and for those that are not authorized, where any residues would arise through environmental contamination or illegal use.

The approach recognizes the importance of a preliminary risk assessment to identify the available data and the data gaps and to help refine the risk questions that drive the analysis. The derivation of the risk questions, a step often known as problem formulation, requires close interaction between JECFA and the risk manager seeking advice (e.g. Codex Committee on Residues of Veterinary Drugs in Food [CCRVDF]). The approach further identifies additional tools and options that may be of value in the evaluation of veterinary drug residues and in the communication of the conclusions on risk to those responsible for risk management. The approach is intended to provide increased consistency and transparency to the evaluation of residues of veterinary drugs while offering greater flexibility and adaptability to changes in technology, science and safety concerns.

An important consideration is that while a decision tree approach based on risk analysis may be anticipated to offer improved flexibility in the evaluation of certain categories of veterinary drugs, the need for sufficient data of adequate quality cannot be overemphasized. However, the decision tree approach may help to identify critical data gaps early in the evaluation and potentially lead to the generation of suitable data that will permit a successful evaluation of the veterinary drug.

The concepts embodied in the paper were discussed by the Committee. The Committee endorsed the proposal in principle and generally agreed with the concepts as presented. The Committee discussed and made recommendations for the draft, while it emphasized the following general and specific comments:

### *General comments*

- It was agreed that at this early stage of development, the concepts presented are more important than detailed considerations of roles and implementation. It was recognized that there is little guidance currently presented to direct when and how decisions are made among the decision tree options.
- Inherent in the conceptual approach is an early interactive dialogue between risk managers and risk assessors that may not be fully reflected in the current organizational structures.
- The Committee further noted the need to coordinate and, wherever appropriate, reference similar and related efforts, to ensure a comprehensive and non-duplicative approach. These efforts include the FAO/WHO joint Project to Update and Consolidate Principles and Methods for the Risk Assessment of Chemicals in Food, decisions of this and other Joint Expert Committees and the FAO guidance document on risk analysis.
- Evaluations by the Committee are based on Good Practice in the Use of Veterinary Drugs as defined in the 17th Codex Procedural Manual. Assessments on the potential risk to human health of exposure as a consequence of other scenarios, such as specified misuse scenarios, would be done only on a specific case-by-case basis. The importance of problem formulation under such circumstances was emphasized.
- Some of the concepts raised were applicable to more areas of chemical risk assessment than veterinary drug residues, and those issues that were cross-cutting should be identified and developed with the respective experts from other bodies.

### *Specific comments*

- The Committee emphasized the importance of clearly presenting the intended purpose of the decision tree approach and identifying the target audiences early in the document.
- The Committee recognized that there are many areas identified in the concept paper that will require additional discussion and development. Aspects related to considerations of acute and chronic exposure were particularly identified as needing development and integration into the decision tree approach.
- There are a number of advanced approaches to risk assessment, such as toxicodynamic modelling, that have not been addressed in the present document. These should be mentioned, even though they may not be readily applicable to the majority of veterinary drugs.

The revised concept paper will be attached as an annex to the meeting report.

The Committee recommended, in the interest of transparency and communication, that the JECFA Secretariat share the concept paper with relevant FAO/WHO bodies, including Joint Expert Committees and Codex Committees, while clearly communicating that this paper is a first step in a long-term project. The Committee further recommended that the JECFA Secretariat convene one or more working groups as appropriate to expand and continue the development of a general decision tree approach for the evaluation of veterinary drugs. Progress in the development of this decision tree approach should be discussed at future JECFA meetings.

The Committee identified the following areas for follow-up work:

- Implementation of proposed steps, such as preliminary risk assessment.

- Approaches for chronic and acute exposure assessments.
- Considerations related to the use of the acute reference dose and associated issues related to short-term exposure.
- Applicability of the threshold of toxicological concern approach to residues of veterinary drugs.
- Exploring ways to leverage resources and increase efficiency with approaches such as work sharing between regulatory bodies and JECFA.
- Specific guidance on the application of the decision tree approach, cross-referenced to the diagrams provided.
- Guidance on the use of default and other data-derived safety factors.
- Applicability of other advanced risk assessment procedures and tools not addressed in the present concept paper.

## ***2.2 Residues of veterinary drugs in honey and possible approaches to derive MRLs for this commodity***

The current Committee considered the guidance regarding honey from the sixty-sixth meeting of the Committee (WHO TRS No. 939, 2006). The sixty-sixth Committee recommended that a paper be prepared by an expert with experience in beekeeping and honey production for the next meeting to consider if a separate approach for honey is warranted and, in such a case, to develop a draft recommendation for consideration at the next meeting. The fifty-second meeting of the Committee (WHO TRS No. 893, 2000) first considered the subject and requested that the 12th Session of the CCRVDF comment on the matter; however, no formal comments were provided.

The Committee recognized that there is substantial production and trade in honey; however, there are very limited numbers of residue (MRL) standards for residues in honey. Honey production figures for 2005 indicate that approximately 1400 tonnes were produced worldwide. Honey production is subject to numerous environmental factors, such as cropping, weather conditions and the impact of pests and pathogens.

### ***Points to consider***

The Committee noted that there were a number of factors to consider in developing a process

to address the need for recommending MRLs regarding the use of veterinary drugs and pesticides for bee health. They include, but may not be limited to, the following points:

- The recommendations must be within the Committee's terms of reference, with adequate flexibility to meet differing conditions and availability of information.
- There is a need to accommodate a robust yet conservative approach to facilitate MRL recommendations and encourage sponsorship for studies that the Committee considers necessary for recommending MRLs.
- The drug is available as a commercial product, and the commercial product containing the active ingredient is currently registered by a national or regional authority.
- Honey production and honey bees in most countries are considered as a minor use and/or a minor species food product, and the availability of active sponsors to provide studies suitable for recommendations on MRLs is likely to be limited.

- Honey is widely used as a sweetener and glazing agent in confectionary products, breakfast cereals and baked goods, in addition to direct consumption of liquid and set honey, and these uses must be accounted for in intake estimates.
- Several substances used to manage bee health are unlikely to raise public health concerns, because intake of residues resulting from effective use are far below internationally established ADIs.
- Some proprietary products are not registered for use in bee colonies, and therefore approved dosages and conditions of use do not exist.
- For a number of substances registered for use by national authorities, no contemporary toxicological evaluation may have been performed, or the review did not result in the establishment of a health-based guidance value, such as an ADI.
- The main groups of substances that typically leave residues in edible bee products are antibiotics (residues in honey and royal jelly) and persistent lipophilic acaricides (residues in wax and propolis).
- Royal jelly should be the subject of a separate and later consideration.
- Residues in both honey and wax need to be considered in exposure estimates. The ratio of honey to wax is typically 9:1.

#### *Substances with an existing ADI and/or MRL in a food-producing animal or food commodity*

The main groups of substances that typically leave residues in edible bee products are antibiotics and persistent lipophilic acaricides. Of the products known to be used for treatment of bee diseases, most, but not all, have a national registration and a JECFA or Joint FAO/WHO Meeting on Pesticide Residues (JMPR) evaluation with an ADI and/or MRL (or the equivalent in national legislation) for either a food-producing animal or other food commodity, and usually the active ingredients are substances with a long history of use.

#### *Substances Generally Regarded As Safe*

Several substances are unlikely to raise public health concerns, because any use in food-producing animals, especially the use in bees, is generally regarded as safe. Examples of such substances include formic acid, lactic acid, oxalic acid, thymol and menthol. In the case of a substance that has clear documentation to support the designation as “generally regarded as safe” by national regulatory authorities and not requiring a MRL, a similar designation can be made. It would require a proviso that equivalence can be demonstrated in honey and that the ADI is sufficient so that no MRL should be required and the ADI is not exceeded. In the case of a new substance not previously considered for registration by national authorities, substances would have to be evaluated as new animal drugs or pesticides and subject to a full food safety risk assessment.

#### *Use of non-approved veterinary drugs or pesticides*

In the situation where a substance is not approved for use in food-producing animals (e.g. chloramphenicol or nitrofurans), no exception for honey would be applied.

#### *Products used in apiculture*

Table 1 contains a list of products used in apiculture.

#### *Suggested tools for data generation*

Where an established ADI exists for use in another species as either a veterinary medicine or pesticide, this would generally require a smaller set of additional data for honey, as an ADI exists.

## 1. Design criteria for residue data studies

Study design for residue determinations must take into account how the residue behaves in honey, as well as the following:

- the number of apiaries involved, representing a variety of honey types;
- number of hives per apiary sampled;
- number of frames per hive sampled;
- number of samples of wax and honey to be taken from a frame;
- number and spacing of time points to describe the kinetics of formation and depletion of honey in the edible products;
- estimates of amounts of surplus honey present at the beginning of, during and after the treatment until the end of the trial;
- scheme for the analysis of individual and bulk samples;
- climatic information for the duration of the trial, including season of the year (e.g. rainfall);
- crops on which bees forage;
- temperature profile within the hive;
- data on honey flow periodicity;
- data on any supplemental feed given to bees;
- data on bee health and bee/parasite mortality during the study;
- a protocol for the analysis of individual and bulk samples;
- studies on storage stability of residues in honey.

The above factors recognize the unique nature of honey, as all the drugs and metabolites collect in the honey, and the only mechanisms for reduction are dilution as more honey is produced, removal from the hive, and photochemical or thermal degradation of the residues in the honey or through such factors as pH and environmental conditions. Bees commonly move honey around the hive as required, and this can lead to significant variations in residue concentration, even across the same frame in all three hive dimensions.

The quality of the data should allow a statistical evaluation to determine the confidence intervals necessary to recommend the setting of MRLs. The data should show with 95% statistical confidence that 95% of all honey samples from treated bees would be below the MRL and that the estimated intake of residues (considering all other sources of intake) remains below the ADI. As the design of the study depends on many factors, it has to be developed on a product-by-product basis, depending on the use pattern.

## 2. Marker residue

The marker residue concept may not be normally or easily applied to honey scenarios. However, it is important to sufficiently identify and, where feasible, quantify metabolites and degradation products in honey.

### *Dietary intake considerations*

The Committee reviewed the adequacy for the estimation of chronic and acute intakes of its currently used consumption figure of 20 g honey/day. When the original food basket of the Committee was established, care was taken to ensure that the consumption figures

protected the preferential eater of foods of animal origin. Based on data that were available, the 97.5th percentile of daily consumption by the consumers of a commodity from a country with a known high consumption of the commodity was chosen. It was also considered necessary to derive figures that would also cover the intake resulting from consumption of processed products containing the raw commodity. For honey, these aspects were not sufficiently addressed at previous meetings of the Committee.

The Committee used a study conducted in 1986–1989 in Germany as a basis for the study of methodological aspects of deducing a figure of daily intake of honey, because in this study consumption data for more than 9000 consumers of honey were available. In addition, more recent data and studies from the United Kingdom, the Netherlands and Germany were reviewed. In the above-mentioned German study, more than 9000 “eaters” of honey had consumed approximately 26 000 portions of honey during a 7-day observation period. The 99.95th-percentile of all portions consumed on one day was approximately 144 g. This percentile may be considered as an estimate of acute intake, although further guidance on this is needed.

In discussing criteria for the establishment of an estimate of chronic intake, it was concluded that such a figure should be derived from the consumption data for the “chronic” eaters only.

In the German study, the 97.5th percentile of consumption by the subgroup who consumed  $\geq 7$  portions in a week was approximately 55 g/consumer per day. The data from the United Kingdom were also based on a 7-day survey and had been published by the Food Standards Agency. These data were available only in an aggregated format, and the number of participants was lower. However, the highest estimated percentiles were not too different from those from the German data. Data from a 2-day survey in the Netherlands had been evaluated and used as a basis for modelling. The obtained results were significantly lower than the estimates that were based on the United Kingdom and German data.

Since the data from the United Kingdom clearly indicated that on a body weight basis infants and young children have the highest consumption, this finding was further investigated. The Committee concluded that this was mainly due to the lower body weight of this group and not to higher consumption. In this context, a recent German survey found that the 97.5th percentile of honey consumption by children 2–5 years of age was 22.1 g/day.

The Committee noted that a consumption figure of 50 g/person per day would most likely protect all groups of consumers; however, further data are necessary to determine whether this figure also sufficiently covers the consumption of products containing honey.

Honey comb, with its original honey content, is consumed by a subgroup of consumers. Many lipophilic substances used as acaricides accumulate in wax. Therefore, the labels of certain registered products warn that wax from bees treated with the products should not be consumed. The Committee concluded that in cases where honey comb can be safely consumed, it would use a honey to wax ratio of 9:1 in the estimation of intakes.

**Table 1. List of Products Used in Apiculture**

Substance	Proprietary product	ADI (mg/kg bw per day)	
		JECFA	JMPR
Acrinathrine	Yes		
Amitraz	Yes		0–0.01
Bromopropylate	Yes		0–0.03
Chlorobenzilate	No		0–0.02
Chlortetracycline	No	0–0.003	
Coumaphos	Yes		<sup>2</sup>
Cymiazole hydrochloride	Yes		
Enilconazol (Imazalil)	No		0–0.03
Erythromycin	No	0–0.0007	
Fenproximate	Yes		
Fipronil	No		0–0.0002
Flumethrin	Yes		0–0.004
Formic acid <sup>1</sup>	Yes	0–3	
Fumagillin	Yes		
Lactic acid <sup>1</sup>	No	Not limited	
Lincomycin hydrochloride	?	0–0.03	
Malathion	No		0–0.3
Menthol <sup>1</sup>	Yes	0–4	
Methyl bromide	No		
Monensin	No	0–0.01	
Oxalic acid <sup>1</sup>	Yes		
Oxytetracycline	Yes	0–0.003	
Paradichlorobenzene	No		
Permethrin	Yes		0–0.05
Propargite	?		0–0.01
Rifampicin	No		
Spinosad	No		0–0.02
Streptomycin/Dihydro-Streptomycin	No	0–0.05	
Sulfathiazole	No	No ADI allocated	
Tau-Fluvalinate	Yes		
Thymol <sup>1</sup>	Yes	Acceptable	
Tylosin tartrate	Yes	0–0.03	

1. Substances considered by many national authorities as generally recognized as safe.

2. Temporary ADI withdrawn in 1980; no ADI allocated in 1990.

### *Recommendations*

In considering the matters of interest noted in this report and the complex and unique nature of honey and honey bees, JECFA may not be able to take any specific approaches without

further guidance from CCRVDF. The Committee therefore makes the following recommendations to CCRVDF:

1. That CCRVDF with the aid of member countries compile a comprehensive list of all veterinary drugs registered for honey production and bee health and develop a priority list of veterinary drugs for use in honey bees to be considered for risk assessment by JECFA.
2. That CCRVDF and member countries be encouraged to provide data on honey consumption, considering both direct and indirect honey intake, for purposes of improved intake assessments as part of the risk assessment for recommending MRLs.
3. That CCRVDF consider extension of good veterinary practice guidelines to include honey production.
4. That the CCRVDF ad hoc Working Group on Methods of Analysis and Sampling consider analytical methods for residues in honey.
5. That the CCRVDF provide guidance on the appropriate percentile for an estimation of acute intake.

The Committee further makes the following recommendation to the JECFA Joint Secretariat:

1. That the JMPR Joint Secretariat be advised of the Committee's report regarding residues in honey and considerations of residues from use of pesticides in honey production and bee health.

### ***2.3 Paper by Millstone et al (2008)<sup>1</sup>. Risk assessment policies: Differences across jurisdictions***

The Committee found of interest the comparison of risk assessment policies in different jurisdictions, including the joint FAO/WHO bodies such as JECFA. The Committee fully agrees on the need for greater harmonization and transparency in the conduct of risk assessment, which are among the purposes of risk assessment policies. The Committee noted that both risk assessment policies and practice of risk assessment evolve over time, and that the methods and principles underpinning the risk assessment work of JECFA and its sister bodies are currently being consolidated and updated, which should ensure greater harmonization. Moreover, expert meetings of WHO and FAO, such as JECFA, are conducted according to well established rules in the respective constitutions of WHO and FAO. In addition, JECFA has embarked upon an activity to increase the flexibility with which it can respond to the needs of the Codex Committees and Member States, with respect to concerns about residues arising from veterinary drugs. The Committee was somewhat surprised at the apparent misunderstanding of some of its practices and procedures as reported in the paper by Millstone et al. It is important that readers interested in the workings of JECFA and its sister bodies seek up-to-date guidance from appropriate sources, such as the Secretariat or the WHO and FAO websites.

There are a number of disparities between the text of Millstone et al. and current practices of JECFA. These include the implication that CCRVDF originated the four-step process of risk assessment and that this was not already routinely in use by JECFA; the historical

---

<sup>1</sup> Millstone E, van Zwanenberg P, Levidow L, Spök A, Hirakawa H and Matsuo M (2008). JRC Scientific and Technical Reports. Risk-assessment policies: Differences across jurisdictions. European Communities, Luxembourg

interaction between committees such as JECFA and the CCRVDF in the evolution of safety factors; the nature of the interaction between CCRVDF and JECFA in the development of policy; and the basis for final agreement of the Codex Alimentarius Commission's position on risk assessment policy.

#### **2.4 No-observed-effect level (NOEL) and no-observed-adverse-effect level (NOAEL): Use in JECFA assessments**

The current Committee noted that the sixty-eighth JECFA (additives and contaminants) (WHO TRS No. 939, 2006) had reconsidered the use of the terms no-observed-effect level (NOEL), no-observed-adverse-effect level (NOAEL) and the related terms lowest-observed-effect level (LOEL) and lowest-observed-adverse-effect level (LOAEL) in evaluations of the safety of food additives and contaminants. Taking into account common practice in other risk assessment bodies, the current Committee decided to harmonize with the sixty-eighth JECFA and agreed to differentiate between the terms NOAEL and NOEL for the evaluation of veterinary drugs in food. The following definitions, based on WHO Environmental Health Criteria, No. 170, *Assessing the human health risk of chemicals: Derivation of guidance values for health-based exposure limits*, were accepted:

**No-observed-adverse-effect level (NOAEL):** *greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or lifespan of the target organism under defined conditions of exposure....*

**No-observed-effect level (NOEL):** *greatest concentration or amount of a substance, found by experiment or observation, that causes no alteration of morphology, functional capacity, growth, development, or lifespan of the target organism distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.*

The Committee noted that it has, up to now, applied the NOEL according to the EHC 70 definition. This definition includes the statement that the NOEL “causes no detectable, **usually adverse**, alteration of morphology, functional capacity, growth, development, or lifespan of the target” [emphasis added]. The Committee emphasized that the current decision to accept the definitions of NOEL and NOAEL from EHC 170 does not entail any change in its evaluation practice. It is merely harmonizing the terminology used to differentiate between observed effects and observed adverse effects. Hence, this decision has no impact on any of the previous evaluations made by this Committee.

## Annex 3

### Seventieth meeting of the Joint FAO/WHO Expert Committee on Food Additives

Geneva, Switzerland, 21–29 October 2008

#### Members

Professor Arturo Anadón, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Spain

Dr Dieter Arnold, Berlin, Germany

Professor Alan R. Boobis, Faculty of Medicine, Imperial College London, England

Dr Richard Ellis, Consultant, Myrtle Beach, South Carolina, USA

Dra Adriana Fernández Suárez, Instituto Nacional de Tecnología Agropecuaria, Buenos Aires, Argentina

Dr Lynn G. Friedlander, US Food and Drug Administration, Rockville, MD, United States of America

Dr Kevin Greenlees, US Food and Drug Administration, Rockville, MD, United States of America

Dr John C. Larsen, National Food Institute, National Food Institute, Technical University of Denmark, Søborg, Denmark

Professor Emeritus J.G. McLean, Camberwell, Victoria, Australia (*Chairman*)

Professor Joao Palermo-Neto, Faculty of Veterinary Medicine, University of São Paulo, São Paulo, Brazil  
Dr Philip Reeves, Australian Pesticides and Veterinary Medicines Authority, Kingston, ACT, Australia

Dr Pascal Sanders, Agence Française de Sécurité Sanitaire des Aliments, Laboratoire d'Etudes et de Recherches sur les Médicaments Vétérinaires et les Désinfectants, Fougères, France

Professor G.E. Swan, Faculty of Veterinary Science, University of Pretoria, Onderstepoort, South Africa (*Vice-Chairman*)

#### Secretariat

Dr Susan Barlow, Consultant, Brighton, East Sussex, England (*WHO Temporary Adviser*)

Ir Astrid S. Bulder, RIKILT Institute of Food Safety – Wageningen UR, Wageningen, Netherlands (*WHO Temporary Adviser*)

Dr Carl Cerniglia, US Food and Drug Administration, Jefferson, AR, United States of America (*WHO Temporary Adviser*)

Dr Pamela Chamberlain, Covance Laboratories, Vienna, VA, United States of America (*WHO Temporary Adviser*)

Dr Myoengsin Choi, Department of Food Safety, Zoonoses and Foodborne Diseases, World Health Organization, Geneva, Switzerland (*WHO Staff Member*)

Dr Bernadette Dunham, US Food and Drug Administration, Rockville, MD, United States of America (*WHO Temporary Adviser; unable to attend*)

Dr Donald Grant, Consultant, Ottawa, Ontario, Canada (*WHO Temporary Adviser*)

Dr Toshio Imai, National Institute of Health Sciences, Tokyo, Japan (*WHO Temporary Adviser*)

Dr Sang-Hee Jeong, Ministry of Food, Agriculture, Forestry and Fisheries, Anyang City, Republic of Korea (*WHO Temporary Adviser*)

Professor Bruno Le Bizec, Laboratoire d'Etude des Résidus et contaminants dans les aliments, Ecole Nationale Vétérinaire de Nantes, Nantes, France (FAO Expert)

Dr Jacek Lewicki, Faculty of Veterinary Medicine, Warsaw University of Life Sciences - SGGW, Warsaw, Poland (FAO Expert)

Dra Betty San Martín Nuñez, Facultad de Ciencias Veterinarias y Pecuarias, Universidad de Chile, La Pintana, Chile (FAO Expert)

Professor Len Ritter, Department of Environmental Biology, University of Guelph, Guelph, Ontario, Canada (WHO Temporary Adviser)

Dr Gladwin Roberts, Consultant, Preston, Victoria, Australia (WHO Temporary Adviser)

Ms Marla Sheffer, Orleans, Ontario, Canada (WHO Editor)

Dr Angelika Tritscher, Department of Food Safety, Zoonoses and Foodborne Diseases, World Health Organization, Geneva, Switzerland (WHO Joint Secretary)

Dr Annika Wennberg, Nutrition and Consumer Protection Division, Food and Agriculture Organization of the United Nations, Rome, Italy (FAO Joint Secretary)

Professor Shi-Xin Xu, Center for Veterinary Drug Evaluation, China Institute of Veterinary Drugs Control, Beijing, China (FAO Expert)