Food and Agriculture Organization of the United Nations

World Health Organization

A Risk-Based Decision Tree Approach for the Safety Evaluation of Residues of Veterinary Drugs

This document is to be considered as 'work in progress'. A first draft was discussed at the 70th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and suggestions for revisions incorporated in this version. This document will be further elaborated through expert working groups and with input of interested parties, in particular through the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF).

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TABLE OF CONTENT

1. INTRODUCTION 3

2. A RISK-BASED APPROACH TO THE ASSESSMENT OF VETERINARY DRUGS 6

2.1 Problem Formulation (Step A) 7

2.1.1 Request for ADI or ARfD and MRL of a Veterinary Drug 7
2.1.2 Request for Advice Regarding Human Health Protection from Contaminants Related to Veterinary Uses 8

2.2 Systematic Collection of Prior Knowledge 9

2.3 Preliminary Risk Assessment (Step B) 10

2.4 Decisions on the Needs for the Risk Assessment (Step B) 10

2.4. Risk Assessment (Step C) 11

2.5 Communication of the Risk Assessment (Step D) 12

2. 5. 1 Codex risk analysis principles 12
2.5.2 Results of Risk Assessment should address the objectives laid out in the problem formulation or identify why that is not possible. 12

3. FORMAL JECFA RISK ASSESSMENT - DECISION TREE APPROACH (STEP C) 13

3.1 Introduction 13

3.2 Collection of Data 15

3.2.1 Formal JECFA call for data 15

3.3 Identification and Characterization of the Hazards 16

3.4 Characterization of the Exposures 18

3.5 Characterization of Risk 19

3.5.1 Health Based Guidance Values 19
Acceptable Daily Intake 19
Acute Reference Dose (ARfD) 19
3.5.2 Pharmacological versus Toxicological Endpoints 20
3.5.3 Safety/Uncertainty factors 21
3.5.4 Adverse effects on human gastrointestinal microbiota 23
3.5.5 Threshold of Toxicological Concern (TTC) 24
3.5.6 Margin of Exposure (MOE) and Margin of Safety (MOS) 26
MOE (Margin of Exposure) 26
MOS (Margin of Safety) 27
3.5.7 Qualitative estimates 28
3.5.8 Management of Risk 28
3.5.8.1 Maximum Residue Level recommendation 28
3.5.9 Identification of strengths and weaknesses in the Risk Assessment (uncertainties and sensitivity analysis) 28

4. COMMUNICATION OF THE RISK ASSESSMENT 31

GLOSSARY 34

1. Introduction

The Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) was created by the Codex Alimentarius Commission as a result of the advice of a 1984 *ad hoc* Joint FAO/WHO Expert Consultation. The Codex Alimentarius Commission also called upon the Directors-General of FAO and WHO to establish an appropriate expert body to provide independent scientific advice to the Commission and its subsidiary body. FAO and WHO subsequently agreed to convene regular joint FAO/WHO Expert Committee meetings to provide such advice to CCRVDF. Residues of veterinary drugs in food have been evaluated by JECFA on an ad hoc basis during regular meetings, however following the request of the Commission, the 32nd JECFA was the first meeting convened expressly to consider residues of veterinary drugs in foods. JECFA as the risk assessment body is independent of Codex and is responsible only to the Directors-General of FAO and WHO, but has a close working relationship with the CCRVDF through the JECFA Secretariat. JECFA provides scientific advice not only to CCRVDF but also to WHO, FAO and their member states.

The current JECFA terms of reference for residues of veterinary drugs are as follows:
JECFA

- Elaborates principles for evaluating their safety and for quantifying their risks;
- Establishes ADIs for chronic exposure and other guidance values for acute exposure;
- Recommends maximum residue limits (MRLs) for target tissues; and
- Determines appropriate criteria for and evaluates methods of analysis for detecting and/or quantifying residues in food.

Following further consideration of the present document, it is recommended that JECFA (and CCRVDF) consider whether any revisions of these terms of reference are necessary.

The basic approach to the evaluation of the safety of veterinary drugs by the JECFA was essentially established in the 1987 document, *Environmental Health Criteria 70*: *Principles for the Safety Assessment of Food Additives and Contaminants in Food (EHC 70)*. The principles described are applicable to all chemicals in food, and some specific considerations are given to residues of veterinary drugs,. The individual approaches contained in this document were, in turn, developed earlier through the 1950s and 1980s with some refinement based on technological advances such as improved physiological measurements, more sensitive analytical methods and the use of radiochemical labeling. The risk assessment principles described in the environmental health criteria documents EHC 70 (WHO 1987) and its companion on pesticide residues, EHC 104 (WHO 1990), have undergone regular updating at meetings of JECFA and JMPR. These environmental health criteria documents are currently undergoing revision within the project to update the principles and methods for the assessment of chemicals in food, to consolidate developments since their respective publication and to harmonize approaches to the extent possible. The overall approach for the safety assessment of food chemicals, as outlined in EHC 70, may be summarized as follows:

For compounds that produce effects for which there is no evidence of a threshold, it is not possible to identify an acceptable level of exposure. Hence, it is normally not appropriate to derive health based guidance values (e.g. ADIs) for such compounds, nor recommend MRLs. The most common compounds that come into this category are carcinogens acting via direct effects on DNA. JECFA at its 64th meeting (WHO 2006) considered risk assessment alternatives for compounds which are genotoxic and carcinogenic and recommended the Margin of Exposure

(MOE) approach, which is the ratio of a defined low effect level observed in experimental studies and the estimated human exposure.

For compounds other than these:

1. Evaluate known endpoints of toxicity including short-term systemic oral toxicity, reproduction and developmental (including fetal development and multi-generation) effects, chronic oral toxicity, genotoxicity, carcinogenicity, neurotoxicity, and pharmacological effects, using animal and human data (limited *in-vitro* data used primarily in predicting genotoxic potential).
2. Determine a no-observed-adverse-effect level (NOAEL[1]) for each of these endpoints of toxicity.
3. Select the most appropriate NOAEL based on sensitivity and relevance as the basis for the calculation of the acceptable daily intake (ADI).
4. Using safety/uncertainty factors, establish an acceptable daily intake (ADI) for chronic human consumption of the veterinary drug residues.
5. Determine the uptake, nature, distribution, and depletion of residues of the veterinary drug in edible tissues.
6. Establish a residue definition comprising parent compound and/or metabolites, based on analytical and toxicological considerations.
7. Establish an analytically measurable maximum residue level (MRL) that will assure that chronic consumption of residues of the veterinary drug in the edible tissues will not result in exceedance of the ADI.

In its assessment, JECFA considers residues of veterinary drugs arising from use according to good practice in the use of veterinary drugs (GPVD). This use of GPVD was elaborated in the report of the 32nd JECFA and has been an underlying principle in the evaluation of veterinary drug residues. MRLs are recommended on the basis of such use, and are not intended to cover misuse or abuse.

The result is an approach that has served remarkably well to protect the public health, resulting in MRLs for 49 veterinary drugs in multiple species and tissues. However, the approach is predicated on the ability to determine a threshold for toxicity (NOAEL), has difficulty in accommodating data gaps (for example lack of a study to address reproductive toxicity or incomplete metabolism data), and unless an ADI and MRL can be determined, it provides no mechanism for the provision of meaningful advice to risk managers.

Increasingly JECFA is being asked to address questions regarding the risk of veterinary drug residues for which there is no full data package. As discussed below, situations where this may occur include "old" drugs, drugs with no commercial sponsor, drugs no longer in use which produce contamination of food because of environmental persistence, or the misuse or abuse of drugs. Current JECFA risk assessment practices need to be adapted to address such issues. Hence, there is a need for a more flexible approach to enable JECFA to respond more effectively to requests related to such substances from CCRVDF, member states, FAO and WHO. This document is the first stage in the development of a decision tree approach, based on the principles of risk analysis, to achieve this goal. A first draft of the document was discussed at the 70th

[1] JECFA has used the term NOEL (no observed effect level) for the reference point (or point of departure) for derivation of the ADI, considering effects that are usually adverse. In order to harmonize with common practice in other risk assessment bodies and with JMPR, JECFA decided at its 68th (WHO 2007) and 70th (WHO 2009) meetings to differentiate between the terms NOEL and NOAEL.

JECFA, where important feedback was received. This version incorporates the suggestions received, to the extent possible. However, it should be emphasized that this is a work in progress, and that there are some components of the strategy which particularly require further development, perhaps most notably on dietary exposure assessment.

A key component of the proposed strategy is problem formulation, which will require close dialogue between risk assessors and risk managers. The approach recognizes the intrinsic ability of a preliminary risk assessment to identify what data are available and where are the data gaps, and to help to refine the risk questions that drive the analysis. It 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, pharmacology, and safety concerns.

The basic approach is derived from the 2003 publication by Renwick, *et al*. This publication presents a decision tree approach for the safety evaluation of chemicals in food. While not specifically designed for residues of veterinary drugs, the publication emphasizes a hypothesis driven risk analysis approach that calls for a close interactive relationship between the developer of the safety data (here the pharmaceutical sponsor), the risk manager (CCRVDF) and the risk assessor (JECFA). As will be discussed later in the current paper, it is hoped that early application of risk analysis principles will help identify what data are available and where any important data gaps are, *prior* to the formal JECFA evaluation. This will, in turn, increase the opportunity to address those data gaps and provide the most useful data package possible for evaluation. It is therefore emphasized that this document is relevant not only to risk assessors and risk managers, but also to data providers. The framework for such an approach is summarized in Figure 1.

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 over emphasized. However, the risk analysis approach may help to identify critical data gaps early in the evaluation, and potentially lead to the generation of critical data that will permit a successful evaluation of the veterinary drug.

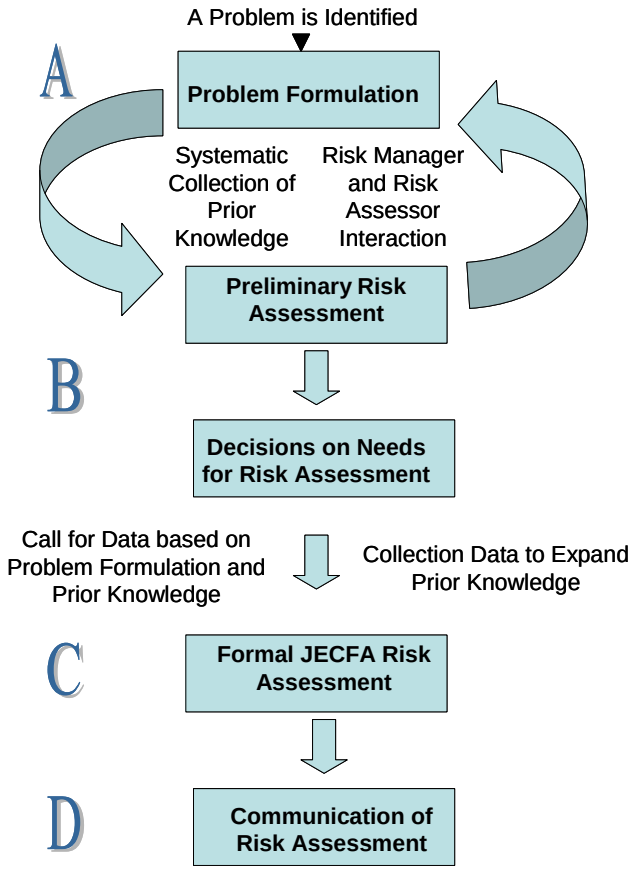

Figure 1. Risk Analysis Framework for the risk-assessment of veterinary drugs

2. A risk-based approach to the assessment of veterinary drugs

Current practice and its limitations

Compounds are placed on the agenda for consideration by JECFA by its secretariat following referral by a number of different possible routes. The main source of requests is the Codex Committee on Veterinary Residues of Drugs (CCRVDF) through the Codex Alimentarius Commission, but requests can also come from member states, from JECFA and its secretariat. The secretariat may independently consider an issue of sufficient concern as to place it on the agenda.

The main question asked of JECFA is what level of residue in food from a veterinary drug would be without health concern. This requires the derivation of a health-based guidance value, usually the ADI, on the basis of toxicological and other relevant data, to be compared to reasonably conservative intake estimates. It also requires the derivation and recommendation of maximum residue limits (MRL) for veterinary drugs in foods based on evaluation of residue depletion and other relevant studies. Recommended MRLs need to be compatible with an acceptable intake, defined as intake without appreciable health risk, when the drug is used according to good veterinary practices. Besides chronic intakes, concerns about the acceptability of short term (acute) intakes, i.e. on a single eating occasion or over 24h, can also exist. An acute health-based

guidance value, the acute reference dose (ARfD), needs to be derived from appropriate acute and short-term toxicity studies and compared to exposure that could reasonable occur following acute or short term (24 h or less) consumption of food with high residue levels. In determining risk from short term intake, it is necessary to use appropriate consumption data, considering short term consumption patterns, large portion sizes and high percentile consumers.

The most common reason for referring a compound for evaluation to JECFA is to obtain recommendations for MRLs for consideration by CCRVDF for veterinary drugs in commercial use internationally. These are usually products with a commercial producer ('sponsor'), i.e. a veterinary pharmaceutical company, who would be expected to generate appropriate data for consideration of the establishment of health-based guidance values and of MRLs. However, the sponsor may not always be a large pharmaceutical company. On occasion, it may be a small commercial organisation, an academic institution or a national government, producing one or a small number of products, more for their essential use in certain parts of the world, than for international commerce. Alternatively, there may be local production by small generics companies of pharmaceuticals no longer under patent, no longer requiring national registration. Sometimes, older drugs have changed producers. As a consequence, the data generated for original registration, generated to protocols and standards now outdated, may be only partially available and of limited utility for a modern evaluation. It is very unlikely that there will be a data package that meets current standards for these products. Nevertheless, JECFA may be asked to consider such drugs for recommendations of MRLs.

In formulating its advice to risk managers, JECFA should endeavour to describe the strengths and weaknesses of the evaluation, and to provide an estimate of the uncertainty in its conclusions. Finally, the JECFA should indicate the potential consequences for human health should specific risk management options not be feasible. This last aspect would require prior discussion with risk managers, as indicated above.

2.1 Problem Formulation (Step A)

Problem formulation is intended to identify and characterize the problem to be addressed, and to determine the risk management goals. In formulating the problem to be addressed by the risk assessment, it is of paramount importance that a dialogue be maintained between JECFA (through the Secretariat) and the risk managers requesting advice. Amongst issues that will need to be resolved are 1) is the compound supported by a commercial sponsor; 2) is the compound registered or likely to be registered in a country or region; 3) is the compound a product of commercial value; 4) is there sufficient information available to enable a meaningful evaluation; 5) what is the specific concern (duration of exposure, population exposed, source of residue in food); 6) are there risk management options available should exposure not be acceptable; 7) what form of advice would be most helpful to the risk manager; 8) if such advice cannot be provided (for example because of data limitations), is there alternative advice that might be of value.

2.1.1 Request for ADI or ARfD and MRL of a Veterinary Drug

In situations where the compound is supported by a commercial sponsor, it is anticipated that registration by national and regional authorities, for example FDA and EMEA in the US and Europe, respectively, would be sought. This would carry with it substantial data requirements, similar to those normally required by JECFA. In such cases, JECFA would anticipate and require that a full data package would be submitted for consideration, and that studies would meet

modern standards. A full data package would comprise results of a comprehensive series of toxicological tests, most of them described by OECD guidelines, to detect general or specific toxic effects, including short- and long-term toxicity, carcinogenicity, genotoxicity, reproductive and development toxicity and other endpoints as appropriate, such as pharmacology, neurotoxicity and immunotoxicity. Information on antimicrobial effects should also be provided, as appropriate. In addition, information on toxicokinetics and metabolism would normally be required. Where the sponsor is not a major pharmaceutical company, registration is likely to be very limited, and data availability would be very variable. While ideally JECFA would expect a full data package, it is recognised that this may not be achievable, due to the limited resources available and the limited commercial return, if any, for such a product. JECFA would consider such submissions on a case by case basis. Similarly, for older drugs, the information available is unlikely to comprise a current, full data package. An example of such a compound is tylosin. In these cases, the information required would be such that it would be possible to address the key questions in the decision tree approach discussed later in this document. Hence, it should be possible to match information on toxicological endpoints with likely duration and extent of exposure and likely exposed populations (e.g. infants). There should be sufficient information on fate in the target veterinary species to enable some estimate of exposure to the human consumer to be derived. It will also be necessary to weigh studies conducted to good laboratory practice (GLP), in which there is full disclosure of the raw data and records to permit detailed evaluation of the study, with studies in the open literature, often not conducted according to any agreed standards, and for which the raw data will not be available, and with studies conducted prior to GLP, and for which the raw data may be available only in part.

2.1.2 Request for Advice Regarding Human Health Protection from Contaminants Related to Veterinary Uses

While most of the questions referred to JECFA relate to the veterinary use of drugs, it is conceivable that there are concerns about the human health effects of pharmaceutical residues in food arising from other situations, such as contamination of livestock with drugs no longer legally used, due to environmental persistence or possible illegal use. Examples where JECFA has undertaken such assessments include chloramphenicol and malachite green. While this is clearly an area that overlaps with the JECFA (additives and contaminants), nevertheless because of its expertise in veterinary medicine, it is likely that on occasion such issues will be referred to JECFA (residues of veterinary drugs). As with “minor use” compounds as described above, it is very unlikely that a full data package will be available. As there may be no sponsor for the compound for any use, JECFA will consider whatever data are available, following a request to do so. Such a request would be made following discussion with JECFA (secretariat) as to the expectations for an evaluation and whether there were sufficient data for the committee to undertake a meaningful evaluation in the first place. As above, there would need to be information such that it was possible to match the toxicological data relevant to the duration and extent of exposure and the likely exposed populations. JECFA would consider the data on a case by case basis and would provide an assessment of the uncertainty in any conclusions regarding acceptability or otherwise of residue levels to which consumers are exposed. When it is not possible to derive a typical health based guidance value such as an ADI or ARfD, due to data limitations, it may still be possible for JECFA to derive a margin of exposure or some other risk estimate (see below). Another situation where JECFA may be asked for advice is abuse or misuse of a compound, such that good veterinary practices are not followed. The route of administration, species, dosage regimen or some other aspect of treatment may not be as approved, but risk managers may wish advice on potential consequences to human health,

2.2 Systematic Collection of Prior Knowledge

The systematic collection of prior knowledge is intended to identify existing information that may contribute to the risk assessment. When considering the assessment of risk for consumption of residues of veterinary drugs, the 32nd JECFA identified the need for the following information to be evaluated:

- General characteristics- details of chemical and physical characteristics of the drug including impurities, purity, and quality of final product. Substances should be registered as veterinary drugs in at least one country (but see above)
- Use patterns – good veterinary or animal husbandry practices including purpose of use, doses, methods of administration, target species, and withdrawal times.
- Pharmacological characteristics
- Analytical criteria
- Metabolism and pharmacokinetics
- Toxicology data
- Residue depletion studies under field conditions

The 42nd JECFA again considered the question of the appropriate data for the human food safety evaluation of residues of veterinary drugs. This consideration was more explicit in the type and design of the studies that would generate the necessary data for evaluation of veterinary drugs.

One of the changes proposed in the current approach is to develop more explicitly the problem formulation for the safety assessment of a particular veterinary drug or chemical in food. Problem formulation, as discussed earlier, is the process in which the safety questions and possible paths to address these questions are identified. An important first step is to identify information that is already available for a preliminary assessment of the veterinary drug, prior to the in-depth review by the JECFA experts. The preliminary assessment provides a tool to identify the strengths and gaps of the existing knowledge base and allows further refinement of the problem formulation.

The nature of the prior knowledge that would be useful in problem formulation and in an initial risk assessment prior to a formal JECFA evaluation does not markedly differ in nature from the information that would be needed for the JECFA evaluation. However, it is anticipated that the systematic collection of available information and initial risk assessment will identify areas where additional information is needed and help to shape the final problem formulation.

Prior knowledge on the substance would be useful in the following areas:

Prior knowledge on identity and use of the substance. This information includes the name and what is known of the physicochemical properties of the substance. It goes further to provide information on the use, or uses of the substance including that as a human or veterinary drug, a pesticide, a human or animal biologic, a human or animal food additive, or other uses. Taken all together, this simply provides a common understanding of what the substance is that is being proposed for evaluation.

Prior knowledge on human exposure to the substance. This information provides the next step in the collection of prior knowledge; having identified what the substance to be evaluated is, this step provides information on the human exposure to the substance. It includes the dose and duration of administration if the substance is used as a human or veterinary drug, but also

includes available information about concentrations of the substance in food or water. In addition, information can be provided about the prevalence of human exposure and the human populations or subpopulations that are exposed.

Prior knowledge on biological effects. This is the information that characterizes the biological hazard presented by the substance. It includes any data on absorption, distribution, metabolism and excretion (ADME) as well pharmacokinetic and pharmacodynamic (PK/PD) information in mammalian species. Information on biological and toxicological effects would include data from *in-vitro* studies as well as studies conducted with humans and other species. Epidemiological information can provide useful information on effects of the substance on human populations. Taken together, this information serves as the basis for a preliminary assessment of the nature of the hazard presented by the substance.

Prior knowledge of evaluations by regulatory authorities. While the JECFA is committed to an independent, scientific evaluation of the safety of the substance in food, it is often useful to consider evaluations by regional and national regulatory authorities, the nature of information available for those evaluations, and what conclusions may have been reached based on the available information. Such considerations may identify additional sources of data, any specific toxicological or other concerns, unique approaches to the evaluation, and help frame the context of the JECFA evaluation.

2.3 Preliminary Risk Assessment (Step B)

A close interaction between risk management and risk assessment during the initial problem formulation, and subsequent systematic collection of prior knowledge, will allow the development of a preliminary risk assessment that will best address the risk management needs.

The preliminary risk assessment should be based on the question(s) identified during the initial problem formulation by risk management. The risk assessment should then proceed to identify and characterize the hazards and exposures, and, if possible provide a preliminary characterization of the risk. It is anticipated that the preliminary risk assessment will be particularly useful in identifying data gaps and other issues that may impact the formal JECFA risk assessment. Continued close interaction between risk management and risk assessment is critical to provide focus and direction for the preliminary risk assessment. The preliminary risk assessment, in turn, may result in refinement of the problem formulation. This interactive process should continue until there is a good understanding of the available information and the impact of this information on the problem formulation. Once agreement is reached between risk management and risk assessment, the results should be used to inform a decision on the needs for a formal JECFA risk assessment and the form it should take.

2.4 Decisions on the Needs for the Risk Assessment (Step B)

The problem formulation, as modified by preliminary risk assessment, will determine the needs for a formal JECFA risk assessment and the form that this risk assessment may take. It is important that the problem formulation results in clear questions to be addressed by the JECFA so that expectations may be met. On the basis of the policy considerations discussed above, the JECFA may be requested, for example, to provide:

- A formal risk assessment to determine a health based guidance value such as an ADI or ARfD and to recommend MRLs. This is the traditional role of the JECFA in support of the CCRVDF.
- A formal risk assessment, recognizing that there are insufficient data to provide an ADI, ARfD, and/or MRL, but intended to identify what data are currently available and to identify the key data gaps. While this has sometimes been the outcome of previous JECFA assessments, it was almost always incidental to an unsuccessful attempt to derive an ADI and recommend an MRL due to data gaps. However, it should be recognized that it may be the stated objective of the risk assessment from the outset, depending on problem formulation.
- A formal risk assessment to provide other estimates of risk to assist risk management decisions.
- An assessment of the risk of more than one risk management option
- A scientific assessment of other issues relating to the safety of the veterinary drug residues for the human consumer.

One result of the preliminary risk assessment is that it will identify data gaps that may help focus the collection of information in the formal JECFA call for data and subsequent literature search. It is also possible that the preliminary risk assessment may identify such data gaps as to lead to a conclusion that it is unlikely that a more formal risk assessment would satisfactorily address the questions posed by the problem formulation. In these circumstances there may be a mutual decision between risk management and risk assessment that the desired risk assessment is not possible at the current time, ideally with identification of those data needs that would enable a risk assessment to proceed. Close interaction between risk management and risk assessment regarding the nature and results of the preliminary risk assessment, should result in a problem formulation that would result in a risk assessment that will adequately address risk management needs.

2.4. Risk Assessment (Step C)

Should the preliminary risk assessment result in the conclusion that a detailed risk assessment is required, a formal risk assessment is conducted in accordance with the general principles of the risk assessment paradigm, which includes four steps:

- hazard identification
- hazard characterization
- exposure assessment
- risk characterization

The purpose of this process is to evaluate the probability and severity of the known or potential adverse effects on health resulting from human exposure to food-borne hazards, in this case human exposure to veterinary drug residues in foods of animal origin. Identification and characterization of hazards typically require thorough assessment, amongst other things, of data from relevant studies as described in section 1 above. In addition, an evaluation of microbial risk is undertaken for those veterinary drugs with antimicrobial activity.

Chapter 3 describes the actual decision tree approach for the risk assessment of veterinary drugs,

2.5 Communication of the Risk Assessment (Step D)

2. 5. 1 Codex risk analysis principles

In the risk analysis principles adopted by the Codex Alimentarius Commission, risk communication is defined as follows in the Codex Procedural Manual (17th ed.)[2]: 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. Furthermore, it is stated that 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.

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, and thus also in the provision of scientific advice on the risks associated with a particular chemical present in food.

From this it follows that the results of risk assessments by JECFA should be explained in a clear and transparent manner, including uncertainties and constraints and how these were managed in the risk assessment process (see above).

2.5.2 Results of Risk Assessment should address the objectives laid out in the problem formulation or identify why that is not possible.

As regards the scope and purpose of a particular risk assessment being commissioned, these should be clearly stated and be in accordance with the risk assessment policy of the relevant Codex Committee, in the case of residues of veterinary drugs the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). The output form and possible alternative outputs of the risk assessment should be defined.

Guidance in the risk assessment policy on the problem formulation of the requests from CCRVDF is mainly related to the development of recommendations on MRLs. It is stated that the report on the risk assessment should clearly identify the choices made during the risk assessment with respect to uncertainties and level of confidence in the studies assessed. If MRLs cannot be recommended, due to lack of data to establish an ADI/recommend MRLs, the data gaps should be identified. If considered necessary, different risk management options could be proposed, and in such cases, these options should be clearly distinguished from the results of the risk assessment itself.

In addition, risk assessments should take into account other relevant information. In the case of those requested by the Codex Alimentarius, this would include 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.

[2] ftp://ftp.fao.org/codex/Publications/ProcManuals/Manual_17e.pdf

The following scheme could be considered, in this order, to describe the outcome of the risk assessment to the risk managers that commissioned the risk assessment, depending on the data availability and the choices made in the course of the risk assessment.

a. Provide Health Based Guidance Value(s) if supported by the Risk Assessment
b. If Risk Assessment does not support Health Based Guidance Value(s)
    i. Provide other estimate of risk
    ii. Describe the data gaps and recommend additional studies
c. Offer additional advice as warranted to the risk managers
    i. Examples such as advice on potential impact of residues that may be considered safe for human consumption on cheese making or other food production processes.

3. Formal JECFA Risk Assessment - Decision tree approach (Step C)

3.1 Introduction

The nature of the risk assessment is determined by the decisions on the needs from the preliminary risk assessment above and availability of critical data

As noted above (see *Introduction)*, the basic approach to the evaluation of safety of veterinary drugs by the JECFA was essentially established in the 1987 document, *Environmental Health Criteria 70*: *Principles for the Safety Assessment of Food Additives and Contaminants in Food* (WHO 1987). While these principles pre-date the formal emergence of the veterinary drug residue assessments carried out by JECFA, veterinary drugs are covered to some degree, and the general approach described in EHC 70 has direct application to these substances. In addition, two recent analyses of the approach have been undertaken, by the CCRVDF in 2001 and by the JECFA in 2006. As explained above, the risk assessment principles described in EHC 70 are currently being revised as part of an IPCS Project to update the principles and methods for the assessment of chemicals in food, available from the WHO website (http://www.who.int/ipcs/food/principles/en/).

JECFA has long recognized that a number of factors can be used to inform the risk assessment; in general (not necessarily specific to residues of veterinary drugs) these include the structure of the chemical, its natural occurrence in foodstuffs, its metabolic characteristics and knowledge of its effects in humans. JECFA requests detailed pharmacology data, and data from drug metabolism and other related studies to identify the specific molecular species of toxicological concern. Generally, identified metabolites that contribute ten percent or more of the total residues are candidates for toxicological evaluation. However, in some instances metabolites consisting of less than ten percent of the total residues have been considered. In addition, JECFA will consider microbiologically active residues in establishing safe levels of exposure.

The proposed formal JECFA risk assessment is presented diagrammatically in Figure 2. The flow chart does not attempt to provide the details of the risk assessment, either for hazard or exposure characterization, as described in the text below. The flow chart rather presents the major steps of the assessment along with some of the key decision points.

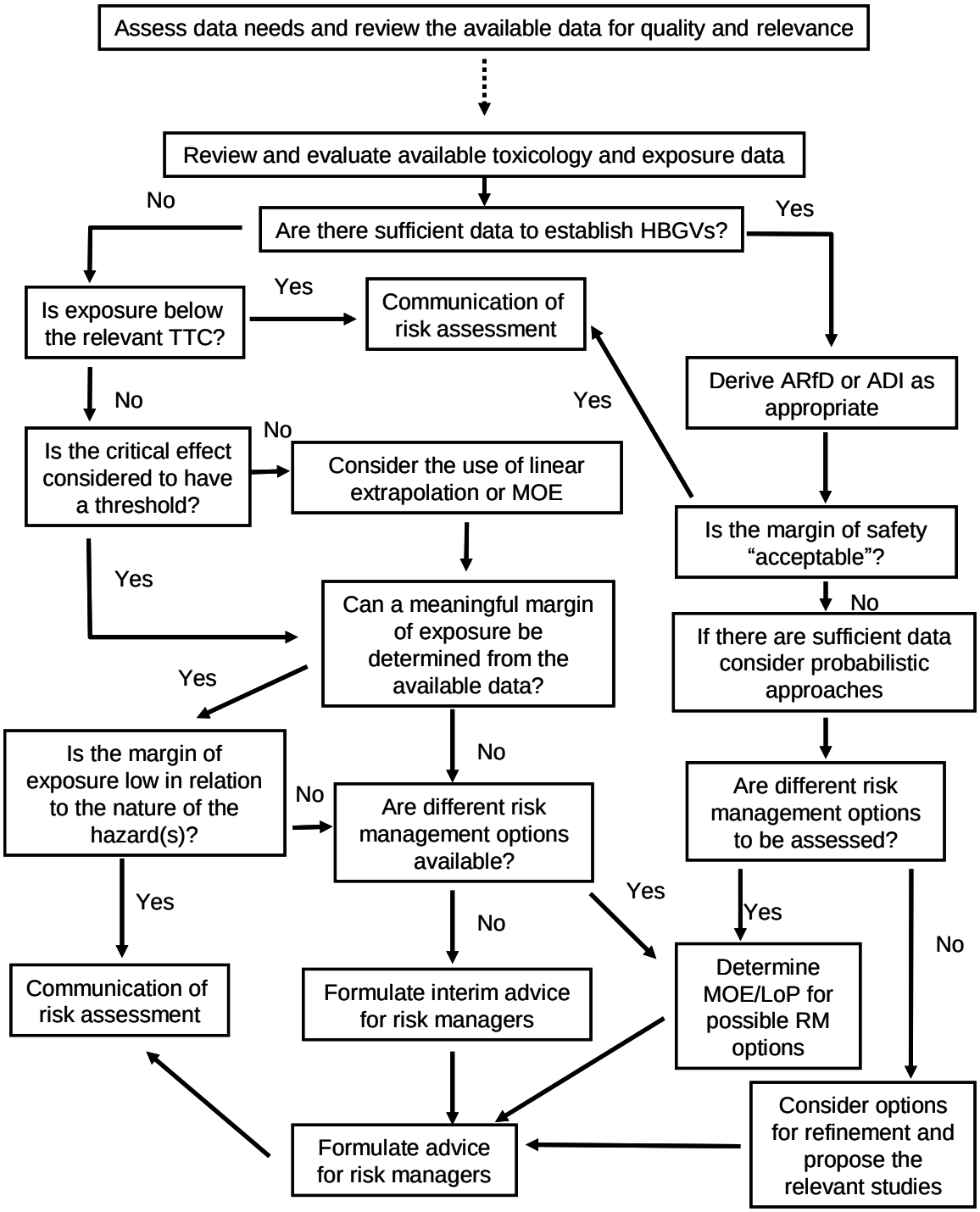

Figure 2. Decision Tree Approach in the Risk Assessment of Residues of Veterinary Drugs.

3.2 Collection of Data

In addition to the collection of prior knowledge conducted as part of the preliminary risk assessment, there is a formal call for data by the JECFA. While the collection of prior knowledge focuses on publicly available information, the call for data focuses on both proprietary and public data, particularly those data that may have been used to support the approval or registration of the veterinary drug with a national or regional authority.

3.2.1 Formal JECFA call for data

Requests for the evaluation of certain veterinary drugs or other relevant substances for which a hazard has been identified, as well as consideration of issues of a more general nature by the Committee may come from a number of sources:

- 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, which are in accord with accepted procedures of the Codex Alimentarius Commission, in particular relating to the risk analysis policy adopted for CCRVDF.
- FAO and WHO Member States may request the inclusion of veterinary drugs on the agenda of JECFA through a direct request.
- 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.
- The JECFA secretariat may place a veterinary drug on the agenda for re-evaluation even though no outside request has been received.
- 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.

Before inclusion of a substance on an agenda for the first time, the JECFA Secretariat will have received a firm indication that there will be one or more submitters of data for the evaluation, or that the data are available from other sources such as a government organization or the published literature. For substances that are being re-evaluated, for example those that have a temporary ADI, the Secretariat assumes that the sponsor of the original evaluation will be providing the necessary data unless informed otherwise. All requests must be associated with a commitment to provide the necessary data 6-7 months before the relevant meeting.

The Joint Secretaries of JECFA distribute an official call for data on the compounds selected for the agenda 10-12 months in advance of the meeting, on the respective JECFA websites at FAO and WHO. In the call, the type of toxicological and residue data that is normally required for a risk assessment of a veterinary drug is detailed. The Call is also advertised through other channels and information is provided to all Codex Contact Points. The deadline for submission of data and information is usually 6-7 months prior to the meeting to allow sufficient time for an assessment.

Details of the process for collection of data are provided in WHO procedural guidelines , "Residues of veterinary drugs in food. WHO procedural guidelines for Joint FAO/WHO Expert Committee on Food Additives" (WHO 2001)[3].

Collection of submitted data

The Joint Secretary will provide those submitting the data with the names and contact details of the individual(s) that have been assigned the responsibility to prepare the working paper for the substances on the agenda. The data are normally sent directly from the sponsors to the experts and joint secretariat.

Expert literature search

The JECFA perform its assessments based on all available data. Accordingly, the expert drafting the monograph should always perform a literature search on the compounds assigned to him or her. It is extremely important that literature searches are performed, especially on veterinary drugs that have been in use for a long time in human and/or animal medicine. This is also the case for substances other than approved veterinary drugs for which requests for a formal risk assessment by JECFA are made. The drafting expert will contact the sponsor and request submission of studies that he or she knows have been reported elsewhere but have not been included in the data package if they are likely to be relevant to the evaluation. If the sponsor is unresponsive to this request, the drafting expert should note the potential impact of the missing data on the evaluation. If full reports of studies are not submitted, the drafting expert will request them, including individual animal data, from the sponsor.

3.3 Identification and Characterization of the Hazards

Includes all available knowledge on biological effects and, when possible, thresholds for those effects

JECFA normally requires sponsors to provide information from a comprehensive series of toxicological tests, most of them described by OECD guidelines, to detect general or specific toxic effects. The effects investigated may also include the pharmacological and microbiological effects that might help characterize the hazards for residues of certain substances such as, for example, antibiotics, hormones, ß-agonists, tranquillizers and anti-inflammatory substances. Where a species-specific metabolite is found in a food producing animal, studies in experimental animals will have provided no information on the toxicological effects of this metabolite. Such metabolites should be dealt with on a case-by-case basis, and this may include the need for some limited toxicological testing of the metabolite itself. Such testing enables the range of effects of the compound to be identified and serves as the basis of hazard characterization. Further details of the toxicity testing of veterinary drugs can be found in the forthcoming EHC harmonizing EHC70 and EHC 104.

The objective of hazard characterization is to determine the relationship that exists between the magnitude of exposure to a chemical agent and the severity and/or frequency of associated adverse health effect in experimental animals. This is defined as the dose-response relationship. The dose-response relationship must be established for each toxicological end-point in each study and aids in the determination of a no observed adverse effect level (NOAEL), for a particular endpoint, in the study. The lowest NOAEL in a study is the study NOAEL. The lowest NOAEL amongst all of the endpoints in all of the studies is often referred to as the critical NOAEL. It may be necessary to identify more than one critical NAOEL, for example for acute and long term

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

effects, or for effects in the general population and in pregnant women. As an alternative to the NOAEL, the benchmark dose (BMD) may be used. This is the dose producing a specified response, the benchmark response (BMR), usually 5% for continuous data and 10% for incidence data, determined by modeling the data. To allow for experimental variation in the data, the lower 95% confidence limit on the BMD is often used. This is referred to as the BMDL. Hence, when the BMR is 10%, the BMDL10 would be used. Guidance on the benchmark approach can be found in the draft EHC document on Principles for Modelling Dose-Response for the Risk Assessment of Chemicals[4].

Discussion of how different kinds of available data may change the direction of the characterization – for example, how relevant human epidemiological data may impact the evaluation

Hazard characterization can be based on observations in humans as well as studies in laboratory animals. In the case of residues of veterinary drugs, however, for the most part it will be based on toxicological studies in laboratory animals. Focused *in vitro* experiments can also contribute to this characterization. Where epidemiological data are available, it may be possible to directly characterize an adverse effect caused in humans following the ingestion of drug residues, without the need to extrapolate from an animal experiment. Although this approach can significantly reduce the inherent uncertainty associated with the use of data from laboratory animals, and the subsequent extrapolation of effects to humans, data on exposure in such studies is typically very limited and uncertain. In addition, the power of such studies makes it almost impossible to be able to identify any adverse effects produced by exposure to the low residue levels typically found in food. This is particularly the case for effects that occur over a prolonged period of time. Revealing allergic effects in humans from penicillin residues is a (un)fortunate exception.

More frequently, it may be possible to obtain useful information for veterinary drug classes that are also used in human medicine. In this case it may be possible to observe adverse effects caused by high doses used when treating humans, but it will still be necessary to extrapolate to the risks associated with the continuous ingestion of much smaller quantities of dietary residues. Studies carried out on humans using drugs that are very similar to those employed in veterinary medicine will provide information on the doses associated with pharmacological effects. However, a limitation of such studies in the risk assessment of residues of veterinary drugs lies in the fact that the purpose of the studies is to determine an optimal therapeutic dose and not a dose without effect. In addition, some human drugs are neither administered nor tested by oral routes of exposure, making extrapolation to effects following consumption of residues in food difficult.

There is increasing scientific and ethical interest in the development of non-animal methods, particularly *in vitro* and *in silico* models, which may replace or supplement animal experiments. Despite the progress made, the results to date are such that few of these tests have yet been validated for use in support of a formal risk assessment. However, they can be particularly valuable in mechanistic studies, such as species comparisons of metabolic profiles or potency comparisons using the molecular target. Some tests are widely used for qualitative characterization of hazards, particularly of genotoxicity. One exception is the use of in vitro tests to quantify antimicrobial effects on human gut microflora.

For the time being, the risk assessment of residues of veterinary drugs will depend mainly upon the results of studies in experimental animals.

[4] http://www.who.int/ipcs/methods/harmonization/draft_document_for_comment.pdf

3.4 Characterization of the Exposures

[Note that this section is in a preliminary stage and requires extensive further work]

Includes all available knowledge on populations exposed, prevalence of exposure, and concentrations in edible tissues.

JECFA uses a model diet as a conservative estimate of average long term consumption, combined with intake at the median residue level. However, the exposure assessment could be refined by utilizing data on specific consumption patterns as reported in the 13 GEMS/Food cluster diets. Acute risk assessment requires an estimate of short term intake of a high consumer (upper percentile, e.g. 97.5th), based on large portion size. JMPR has developed detailed methodology for this purpose (JMPR, 2003[5]). While JMPR may use a variability factor to take into account inter-unit variation around the MRL or STMR (supervised trials median residue), consideration would need to be given as to the appropriate estimate of intake of a residue of a veterinary drug, under such circumstances.

While intake of residues of most veterinary drugs assessed by JECFA is based on the median residue level, there may be situations where this is either not appropriate or possible. Examples would include compounds that are not approved as veterinary drugs but are being considered as contaminants, e.g. malachite green, for which no MRL will be recommended, or drugs with no major sponsor, where the data package is of insufficient quality to support recommendation of an MRL. It is also possible that CCRVDF or a member state may request JECFA to consider specified misuse or abuse scenarios. In all of these situations, an estimate of intake based on other than the median residue level will most probably be required. Appropriate methodology will need to be agreed for this purpose. In the last situation (misuse or abuse), it may be possible to assess intake at multiples of the MRL.

The TTC approach (see below) depends upon reliable estimates of exposure. These may be based on a worst case scenario or the plausible high consumer. Either deterministic or probabilistic methods could be utilized for this purpose.

Level of Protection

The Level of Protection (LoP) is the percentage of the population in whom estimated exposure is below a health based guidance value (i.e., reference dose). The LoP is of value to explore the consequences of different exposure assumptions or risk management options.

The Committee normally utilizes point estimates of exposure, based on a model diet developed for this purpose, for risk assessment of residues of veterinary drugs. However, estimation of the LoP would require construction of a distribution of estimated exposures, based on actual consumption data. Residues data could be either realistic worst case or actual, for example from routine monitoring studies, depending on the question being addressed. The choice of centile for the LoP is a risk management decision and there has been no discussion to date with respect to exposure in a global or even regional population as to what a suitable value might be. At the national level, values of >99% are often used, such as 99.9 or 99.99%. For JECFA to utilize the LoP would require adequate information on regional consumption patterns of food likely to contain residues of veterinary drugs.

[5] http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/Download/2003.pdf

3.5 Characterization of Risk

3.5.1 Health Based Guidance Values

Acceptable Daily Intake

The acceptable daily intake (ADI) is determined by the application of a suitable safety factor (also known as an uncertainty factor) to the lowest, toxicologically relevant, NOAEL. The setting the acceptable daily intake (ADI), the quantity of residues that can be ingested daily over a lifetime by the consumer without appreciable health risk, can be considered as the final stage of the hazard characterization step.

As noted above, the ADI is considered to be the quantity of residues that can be ingested daily over a lifetime by the consumer without appreciable health risk. JECFA does not consider it possible to estimate an exposure without appreciable health risk for compounds that produce effects without a biological threshold, for example DNA-reactive carcinogens. Hence, JECFA typically, does not use mathematical models to extrapolate risks of such compounds to low doses and determine a so-called "virtually safe" dose.

For those effects for which there is evidence of a biological threshold, JECFA then uses a safety factor approach for the derivation of the ADI. The ADI is obtained by identifying a NOAEL (or BMDL) for the critical endpoint from studies in experimental animals (occasionally from studies in humans) and dividing this by a safety factor to derive the corresponding ADI for consumers. A NOAEL is, broadly, the highest dose in a toxicological test that did not cause a statistically significant adverse effect in the laboratory animals.

The estimation of an ADI (same as Reference Dose RfD) is applicable both to substances likely to cause adverse effects following acute (such as the case for penicillin) exposure and to those for which chronic exposure is required to produce the adverse effect. This is a consequence of the definition of the MRL for the residue of a veterinary drug and the way in which exposure is currently assessed. However, in specific circumstances, it may be appropriate to derive an acute reference dose (ARfD), as discussed below.

Acute Reference Dose (ARfD)

The concept of the acute reference dose developed from a consideration of the risks to consumers of exposure to residues of pesticides. As with residues of veterinary drugs, residues of pesticides are regulated by ensuring that residues in food (in this case crops) for human use are not greater that the maximum residue limit (MRL), which is based on pesticide use according to good agricultural practice. In general, pesticides will not be approved for crop use if they produce detectable residues and the residues are such that intake calculated assuming residue levels found in supervised trials (which are based on maximum use according to GAP) exceed the ADI. Residue levels in crops are estimated on composite samples, usually pools of several commodity items (e.g. 10 apples). Hence, it is the average residue level that is used to estimate the acceptability of intake.

It was recognised over the last decade and a half that there can be appreciable inter-unit (commodity) variability in pesticide residue levels, for example in carrots or apples. Intake from a

single commodity item with the highest residue in a batch for which the composite value was still acceptable could give rise to an intake that exceeded the ADI. This led to concern as to the potential risk to consumers posed by such exposures. The exposure of concern is to a single commodity item with an extreme residue level, and this would be a rare occurrence in an individual. Hence, it was recognised that the ADI is not an appropriate health based guidance value for use in such risk assessments, as it assumes exposure at this level every day over a lifetime. Further, the nature of the effect upon which the ADI is based is often such that it is manifest only after exposure for a prolonged period. An alternative health based guidance value was required, reflecting the potential acute effects of the compound, the acute reference dose (ARfD). However, the typical database for a pesticide does not contain information well suited to the reliable identification of such effects.

JMPR recommends that when assessing the need for an ARfD, the entire database should be reviewed using a weight-of-evidence approach, to determine 1) whether any acute effects are observed, for example in acute neurotoxicity studies or on observation of animals after a single dose in a multi-dose study and 2) whether adverse effects seen in repeat dose toxicity studies might be relevant to single exposures. In so doing, consideration needs to be given as to which endpoints indicative of target organ toxicity can be used for setting an ARfD and which of these endpoints could possibly occur after a single exposure.

JMPR has published guidance on the derivation of an acute reference dose. It has identified a number of endpoints that should be given careful consideration as to their relevance to acute exposure. These are the following:

- Haematotoxicity including methaemoglobin formation and haemolytic anaemia.
- Immunotoxicity, which might conceivably be elicited by a single exposure.
- Acute neurotoxicity, including delayed neuropathy, behavioural effects and inhibition of acetylcholinesterase.
- Liver and kidney toxicity, observed in single studies or early in repeated dose studies.
- Endocrine effects with hormonal or other biochemical alterations observed in single dose studies or early repeated dose studies.
- Developmental effects, e.g., resorptions, malformations, other effects on the offspring.

JMPR considers that direct effects on the GI tract/stomach need to be assessed carefully to determine their potential human relevance, for example are they due to local irritation (physical effect) or a biological action (e.g. at a receptor) of the substance; are they related to the method of administration (e.g. with gavage bolus dosing but not when given in the diet). For example, diarrhoea and vomiting in dogs should not be considered relevant for setting an ARfD when these effects are a consequence of high concentrations due to the method of administration (e.g. as a bolus in a capsule or by gavage) and a direct local (irritant) effect.

3.5.2 Pharmacological versus Toxicological Endpoints

In considerations of the acute effects of residues of veterinary drugs, a distinction is often made between pharmacological and toxicological effects. These terms are a likely source of confusion. Axiomatically, the pharmacological effect of a pharmaceutical drug is the biological effect for which it is used therapeutically or prophylactically. This may be acute or long term. Pharmaceutical drugs can produce their effects by acting at any one of a number of molecular

targets, which include receptors, enzymes and ion channels. A toxicological effect is a biological effect with detrimental consequences to survival, reproductive capacity, or ability to respond to other stressors, for the organism or its future progeny. The biological effect of therapeutic benefit in the target species may be undesirable in a consumer, e.g. beta adrenoceptor blockade, and hence would properly be considered a toxicological effect. Nevertheless, in considering the acute effects of residues, a pharmacological effect is normally considered a short term, reversible effect via interaction with the molecular site of action in the target species where it is the desired site of action, such as a receptor, enzyme or ion channel. Generally, anti-microbial effects are excluded from this 'definition'. Toxicological effects are either longer term effects, or off-target effects. It is important to recognise that when considering potential acute effects, off-target effects may still be relevant, for example reversible interaction with an ion channel other than the one targeted for therapeutic purposes.

The distinction between pharmacological and toxicological effects in this context is not helpful in human health risk assessment. JECFA considers all acute effects in terms of the duration of exposure necessary to produce a response, the nature of the effect and the reversibility of interaction with the molecular target. The therapeutic target in target species can be of value in identifying potential effects of concern in exposed consumers.

The ARfD is derived using a similar process to that described above for the ADI. The critical NOAEL or BMDL for an acute effect (or an effect that may be acute) is identified and divided by a safety factor, using similar considerations as those discussed above.

Risk assessment of short term exposure to pesticide residues requires not only a different health based guidance value (the ARfD) to that for long term exposure, but also a different estimate of dietary exposure. For pesticide residues, rather than the international estimate of daily intake, in which a degree of 'averaging' of consumption takes place, the international estimate of short term intake is used, which allows for consumption of a single commodity at the high percentile of the reported distribution, together with 'background' consumption of the rest of the diet, including other commodities.

For residues of veterinary drugs, the problem of inter-unit variability does not arise, due to the nature of sampling of food animals and the distribution of residue within the animals. There are occasional exceptions to this, for example the injection site will often have higher residue levels than in the rest of the animal, and will not be represented by residue levels measured in 'routine' samples. However, in general the need for an acute reference dose for residues of a veterinary drug is not dependent on the needs of the monitoring programme. Nevertheless, there are toxicological reasons why it might be desirable to derive and report an acute reference dose. Consumers may be exposed to residues such that intake for a short time is above the ADI, for example because of lack of adherence to GPVD, or because of non-veterinary use leading to residues in food. Availability of a value for the ARfD would enable the risk manager to make informed decisions and to provide science-based advice to consumers.

However, risk assessment of short term exposure to veterinary residues would require not only an acute reference dose, but also some estimate of short term intake, rather than the current practice of using a model diet.

3.5.3 Safety/Uncertainty factors

The default value of the safety factor, or more appropriately called uncertainty factor, used to

calculate an ADI (or ARfD) from a NOAEL or BMDL is 100. This incorporates allowance for uncertainty and variability in extrapolating from an experimental species to sensitive humans. The default factors for these are 10 for inter-species differences and 10 for inter-individual variability within the human population, the product of which gives a combined factor of 100 (10 x 10). Where the NOAEL or BMDL used as the basis of the ADI has been identified from studies or observations in humans, the factor for inter-species differences is not required. The numerical values of these factors have been discussed in detail elsewhere. In general, they are considered science-based.

The possibility that the sensitivity of individuals in specific sub-populations may vary by more than 10-fold from the average healthy adult should always be considered in the risk characterization step. However, available evidence suggests that the default uncertainty factors currently used are adequately protective of a wide range of individuals within the population, particularly when combined with conservative assumptions in the exposure assessment.

On occasion additional factors may be used, for example to extrapolate from a LOAEL to a NOAEL, from sub-chronic to chronic exposure, for the severity of the endpoint and for incompleteness of the database. These are a mixture of science and policy-based factors. Where a NOAEL cannot be identified, it may still be possible to derive an estimate of the BMDL, thus avoiding the need for an additional factor to extrapolate from the LOAEL.

While the default approach allows for the use of data from either experimental animals (normally, safety factor of 100) or humans (normally, safety factor of 10), it does not allow quantitative incorporation of specific information on toxicokinetic or toxicodynamic differences for a chemical, either between or within species, in the risk assessment. To overcome this limitation, IPCS recommended that the two 10-fold factors for interindividual variability and interspecies extrapolation each be further subdivided into toxicokinetic and toxicodynamic sub-factors. The sub-factors agreed were 4-fold and 2.5-fold for inter-species toxicokinetic and toxicodynamic differences, respectively and 3.16 ($10^{1/2}$) for both human interindividual toxicokinetic and toxicodynamic differences. The resulting sub-factors were termed default subfactors (uncertainty factors or UFs) (WHO, 2005). Where available, information on one or more specific sources of variability and uncertainty could be used to enable derivation of one or more chemical specific adjustment factors (CSAFs), replacing the defaults. The overall or combined uncertainty factor (CUF, equivalent to the safety factor as used by JECFA) is obtained from the product of the CSAFs, using defaults for those sub-factors for which chemical specific information is not available (WHO, 2005).

CSAFs enable information on inter-species or human interindividual differences in the toxicokinetics or toxicodynamics of a specific chemical to be incorporated into the risk assessment. However, such information is often not available, but information on pathways of elimination or mode of action may be available. As information is available on the extent to which some of these pathways or processes vary between or within species, an approach has been proposed to enable this information to be utilised to inform the choice of safety factors (Renwick and Lazarus, 1998). This approach is therefore somewhere between the normal default (100-fold safety factor) and the derivation of CSAFs on the basis of chemical-specific information. Such factors have been termed categorical factors (Walton et al., 2001). JMPR has used this approach to modify the safety factor used for some carbamates, on the basis that their effects depend upon Cmax, and this varies less between species than CL or AUC, variation in which underpins the default values for the safety factors normally used (FAO 2009).

3.5.4 Adverse effects on human gastrointestinal microbiota

As part of its assessment, JECFA considers possible adverse effects of antimicrobial drug residues on human gastrointestinal microbiota. JECFA has consistently taken into account the antimicrobial properties of veterinary drugs where these become the determining factor in the safety evaluation, because the toxicity of some antimicrobial drugs is such that their residue in foods, from a toxicological perspective, could be tolerated at antimicrobially effective tissue concentrations. Of particular concern has been the issue of whether or not residues of these substances ingested in foods pose a danger to human health by exerting a selective pressure on the intestinal microbiota, resulting in a microbial environment that favors disruption of the colonization barrier or the growth of microorganisms with natural or acquired resistance. There are special food safety concerns for the residues of antimicrobial drugs arising from their therapeutic use, as even at these levels they can cause adverse effects on the human intestinal microbiota. Changes to the normal intestinal microbiota due to antimicrobial exposure can lead to reduced colonization resistance, allowing colonization by enteric pathogens, such as *Salmonella* spp., *Campylobacter* spp. and *Escherichia coli*, leading to increased susceptibility to other bacterial infections. In addition, continuous exposure to veterinary antimicrobials may also exert a selective pressure on the intestinal microbiota, favoring the growth of microorganisms with natural or acquired antibiotic resistance. For these reason, JECFA is concerned about the possibility that consumption by humans of small quantities of residues of veterinary antimicrobials in meat might adversely alter the normal human intestinal microbiota. JECFA normally requires all available data on the microbiological activity of a substance and an evaluation report relating such data to possible effects on the human intestinal microbiota. These investigations may be based on the results of studies using *in vivo* or *in vitro* models and/or other relevant data.

A JECFA decision tree approach that complies with VICH GL36 is currently being used by the Committee to determine the need to establish a microbiological ADI for the evaluation of residues of veterinary drugs (WHO 2009). The decision tree approach initially seeks to determine if there may be microbiologically active veterinary drug residues entering the human colon. If the answer is "no" to any of the first three steps, then no microbiological ADI is necessary. However, should such residues be present, then two endpoints of public health concern are to be considered 1) disruption of the colonization barrier and 2) increase of the population(s) of resistant bacteria. At Step 4 of the decision tree process, it is possible to provide scientific justification to eliminate testing (i.e. the need for a microbiological ADI) for either one or both endpoints. Step 5 is where a microbiological ADI would be determined. Should a microbiological ADI not be necessary, then the toxicological ADI would be used. The Committee evaluates data generated from the sponsor and the scientific literature and uses the microbial effects decision tree to answer the following questions in the assessment of veterinary drug residues.

A Decision Tree for Assessment of Microbiological Effects on the Human Intestinal Microflora - Steps in determining the need for a microbiological ADI (derived from VICH GL 36).

- *Step 1*: Are residues of the drug, and (or) its metabolites, microbiologically active against representatives of the human intestinal flora?
- *Step 2*: Do residues enter the human colon?
- *Step 3*: Do the residues entering the human colon remain microbiologically active?
- *Step 4*: Is there any scientific justification to eliminate testing for either one or both

- *Step 5*: 1.) Determine the NOAECs/NOAELs for the endpoint(s) of concern as established in Step 4;
  and
  2.) The most appropriate NOAEC/NOAEL should be used to determine the ADI_{mic}.

The ADI for the veterinary drug is generally chosen from the more conservative ADI, typically the lower of the toxicological and microbiological ADI.

3.5.5 Threshold of Toxicological Concern (TTC)

The objective of the majority of risk assessments is to establish safe intake levels for chemicals. The Threshold of Toxicological Concern (TTC) is a concept that refers to the establishment of a level of exposure for all chemicals, whether or not there are chemical-specific toxicity data, below which there would be no appreciable risk to human health (Kroes 2004). A major advantage of the TTC concept is that it presents a method for enabling resources to be focused on those public health problems that are of greatest potential significance.

The knowledge that toxicity is a function of chemical structure and of the extent of exposure is the basis of the concept of the TTC, and the TTC approach can be used to facilitate risk assessment of substances present at low levels in the diet for which there are few or no compound-specific toxicity data. The approach is based on the concept that a human exposure threshold value can be determined for substances, below which there is a very low probability of any appreciable risk to human health (Munro et al., 1996). The TTC concept has been developed and refined over the last two decades.

Exposure thresholds have been developed for different structural classes of chemicals. A general threshold of 1.5 µg/per person/day has been proposed (Kroes et al, 2004) for compounds excluding those with structural alerts for genotoxicity. This threshold is applied in the US when regulating compounds that can migrate from food contact material.

Subsequent analysis of a large number of compounds for which there was no evidence of carcinogenicity was undertaken on the basis of structural features, according to the scheme of Cramer et al. (1978). This grouped compounds into three classes, class I (simple structures efficiently metabolized to innocuous products), class II (intermediate structures, no positive indication of toxic potential) and class III (complex structures; metabolism to reactive products suggestive of potential toxicity).

Munro et al. (1996) plotted the distribution of NOELs for 600 chemical substances that included food additives, drugs, industrial chemicals and pesticides, arranged according to the three structural classes of Cramer et al. (1978). The 5th percentile of the distribution of NOEL values was calculated for each of the three structural classes. These 5th percentile NOELs were then transformed into human exposure threshold values, referred to as TTCs, by dividing the 5th percentile NOEL for each structural class by a 100-fold uncertainty factor. The resulting TTC values for the structural classes I, II and III of Cramer were 1800, 540, and 90 µg/person per day respectively.

JECFA developed a decision tree for the assessment of flavours based on the TTC concept and applying these TTC values for the three structural classes (Renwick 2004). Over 1700 flavours have been evaluated via this procedure to date.

Kroes et al (2004) reported a detailed analysis of specific sub-groups of chemicals including neurotoxicants and teratogens. It was concluded that no specific considerations were necessary for teratogens but that amongst neurotoxicants, the organophosphates formed a sub-group of their own for which the TTC was 18 µg/day.

Kroes et al. (2004) developed a decision-tree for the application of the TTC concept for substances in structural classes I, II and III, including these new insights. The decision-tree also includes a TTC for potential genotoxic carcinogens, based on the carcinogenic potencies associated with 730 compounds, mostly drawn from the Gold et al. (1989) carcinogenic potency database (Gold & Zeiger, 1997). Analyses by Cheeseman et al. (1999) had indicated that the TD50 values for different structural alerts could be used to identify the most potent genotoxic carcinogens. Kroes et al. (2004) incorporated into their decision-tree (Figure 9.1) a TTC value of 0.15 µg/person per day for those compounds that contained certain structural alerts for genotoxicity. They excluded substances with aflatoxin-like, azoxy- and nitrosamine groups (the so-called 'cohort of concern'), because such substances would give a high probability of a theoretical lifetime cancer risk greater than 1 in 1 million at such an intake, whereas other substances with structural alerts for genotoxicity would present a 95% probability of less than 1 in 1 million risk. They also excluded metals and metal-containing compounds and proteins, because the database from which the TTC values were derived did not include these types of substances.

One final consideration was when there is potential for bioaccumulation. The TTC approach is considered inappropriate where there are marked species differences in the half-life of long lived compounds, amongst which are polyhalogenated- dibenzodioxins, -dibenzofurans and –biphenyls.

There are a number of issues that need to be considered before utilising the TTC approach for residues of veterinary drugs. First there are considerations in relation to exposure. Since the TTC approach compares human exposure threshold values with exposure data, it requires sound estimates of human exposure, and considerations have to be given to acute versus chronic exposure. Second the chemical nature of the compounds considered by JECFA needs to be considered and whether they fit in the structural classes described above. The Cramer classification is based on the concept that specific structural features dictate toxicological potency. Studies need to be undertaken to investigate the suitability of these structural classes for veterinary drugs by analysing the existing toxicity data for such compounds. Of note, and of particular relevance for residues of veterinary drugs in food, the decision tree is based on compounds for which exposure was only by the oral route.

3.5.6 Margin of Exposure (MOE) and Margin of Safety (MOS)

MOE (Margin of Exposure)

Many of the drugs evaluated by JECFA will be registered in a number of countries and regions in the world. They will be supported by a complete data package and the concern of the risk manager is to regulate residue levels such that maximum potential exposure via food from animals treated according to good veterinary practices (GPVD) is acceptable on the basis of a full evaluation of the toxicology, including as necessary antimicrobial risk. As do many other risk assessment groups, JECFA uses a deterministic approach for this purpose, comparing a health based guidance value (the ADI, occasionally the ARfD) with intake by a high consumer, estimated on the basis of the MRL and a model diet. Health based guidance values (ADI and ARfD) are derived from the reference point (e.g. NOAEL, BMDL10) for the most sensitive, relevant toxicological endpoint, usually from a study in experimental animals, although occasionally from studies or observations in humans. As described above, in deriving a health based guidance value, allowance has to be made for uncertainty and variability in extrapolating from an experimental species to sensitive humans, for which safety or adjustment factors are used.

The reporting of a health based guidance value to the risk manager is a strong statement of the confidence in the database. It is implicit that the database is sufficiently robust and comprehensive that all relevant endpoints can be covered by the health based guidance value reported. However, there may be situations where this is not the case, where there are substantial deficiencies or uncertainties in the data such that it is not possible to derive a health based guidance value with confidence. Nevertheless, the risk manager may still require advice, for example where exposure is to a residue from other than the controlled use of a veterinary drug. In such instances, on a case by case basis and following discussion with the risk manager as appropriate, JECFA may report a margin of exposure (MOE).

An alternative situation is where a compound is genotoxic and carcinogenic. While such substances would not normally be acceptable for use as veterinary drugs if they give rise to detectable residues in human food, there may be some situations where JECFA is requested to provide advice following exposure to such compounds in the diet. Examples would be illegal use, former use leading to residues as contaminants, impurities or metabolites in drugs which are not themselves genotoxic and carcinogenic. The 64th JECFA (WHO 2006) developed recommendations on the MOE approach and applied it to several such compounds, to enable the provision of advice.

The MOE is derived by taking the ratio of the reference point (e.g. NOAEL, BMDL10) for the most relevant, sensitive endpoint to an estimate of intake by a high consumer. For compounds that are genotoxic and carcinogenic, it is generally not considered possible to establish a threshold and the use of the NAOEL is not appropriate. For such compounds, where a BMDL cannot be determined, the T25 (the chronic daily dose in mg per kg bodyweight which will give 25% of the animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard life span of that species) (Dybing, et al. 1997) may provide an alternative point of departure. However, the suitability of the T25 for a given data set needs to be considered on a case by case basis.

Where the toxicological database is incomplete, it should be noted that the most sensitive endpoint might not have been evaluated. Further, it might not be possible to derive an MRL for the substance, in which case exposure will need to be estimated from available residues data,

using the same principles as used for deriving an MRL, to the extent possible. The MOE is then reported as a numerical value, with a narrative, emphasising the applicability of the MOE, for example with respect to duration of exposure, type of endpoint, nature of diet, due to limitations in the database used in its derivation. There should also be a discussion of the interpretation of the MOE. In general, the acceptability of an MOE is based on similar considerations to those used in the derivation of a health based guidance value. Hence, when based on data from experimental animals, as a default an MOE of at least 100 would be considered acceptable for effects with a biological threshold. For effects without a threshold, JECFA (additives and contaminants) has suggested an MOE of greater than 10,000. In interpreting the MOE consideration needs to be given to all relevant factors, including the conservatism of assumptions, the completeness of the database (have all potentially relevant endpoints been assessed), whether the response might reasonably be considered to exhibit a biological threshold and whether residues arise through permitted use, inadvertently or unavoidably. These need to be clearly described in the report.

JECFA will generally report an MOE only when there are deficiencies in the database such that it is not possible to derive a health based guidance value with confidence or when the nature of the endpoint is such that derivation of a health based guidance value is not appropriate. Hence, when an MOE is provided by JECFA, it should not be considered a reliable estimate of the acceptability of exposure. However, values of the MOE well above the "target" value provided in the narrative by JECFA can provide some assurance to the risk manager. The MOE is invaluable in evaluating the effectiveness of risk reduction strategies, of comparing different strategies and in assessing the consequences of misuse of abuse of a veterinary drug.

MOS (Margin of Safety)

The margin of safety (MOS) is defined in a similar way to the MOE, but it utilises a health based guidance value (i.e. ADI or ARfD) in the numerator. Hence,

MOS = HBGV (ADI or ARfD)/Estimate of intake

MOS = margin of safety
HBGV = health based guidance value
ADI = acceptable daily intake
ARfD = acute reference dose

When the MOS is less than 1.0, this would raise concerns about the adequacy of consumer protection.

In contrast to the MOE, uncertainty and variability are implicit in the calculated value for the MOS, as they are taken into account in determining the HBGV. As a consequence, the way in which the risk manager interprets the MOS will differ from that for the MOE. As discussed above, JECFA will not establish a health based guidance value unless a sufficiently robust database is available. It therefore follows that it would be possible to determine a margin of safety only in such circumstances. Hence, the primary value of the MOS is in benchmarking actual exposure with respect to the HBGV. For example, this would be of value of assessing the consequences of misuse of abuse of a veterinary product. JECFA may be requested to provide advice on the consequences of scenarios other than GPVD, such as environmental exposure to a veterinary drug as a contaminant, or as a result of specific misuse of abuse. In the event that a HBGV existed or could be determined, the MOS would be of value in formulating such advice.

Interpretation of the MOS requires similar considerations as for the MOE, e.g. what is the toxicological basis of the HBGV, how steep is the dose-response curve, what duration of exceedance of the HBGV is anticipated, by what margin is the MOS less than 1.

3.5.7 Qualitative estimates

In providing comprehensive guidance to risk managers on estimates of risk, it is recognized that there may be circumstances in which neither a quantitative estimate of risk, nor a health base guidance value may be determined. Nevertheless, it may be possible to inform risk management decisions based on qualitative estimates of the risk.

3.5.8 Management of Risk

[Note that this section is in a preliminary stage and requires extensive further work]

3.5.8.1 Maximum Residue Level recommendation

The current draft does not provide a discussion of MRLs. This will be provided in a later version, including similar descriptions of current approaches and possible options, as currently provided in the sections on toxicology above. Issues that will be addressed include:

- MRL/MRLVD definition and derivation
- Incorporation of Good Practices in Veterinary Drug in derivation of MRL
- TMDI and EDI
- Use of current consumption values; use of regional values; chronic vs acute consumption values

3.5.9 Identification of strengths and weaknesses in the Risk Assessment (uncertainties and sensitivity analysis)

Identification and evaluation of the assumptions and sources of uncertainty in a risk assessment are important in ensuring transparency and promoting consistency in risk assessment. The Codex Working Principles for Risk Analysis state that: "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."

It is clearly not feasible, or indeed necessary, to quantify all sources of variability and uncertainty in a risk assessment. Where qualitative consideration of a source of uncertainty provides sufficient confidence (e.g. the assessment is clearly conservative) to enable risk managers to reach a decision, then quantitative assessment would be unnecessary.

A flexible, tiered approach to the evaluation of uncertainty is therefore recommended:

- All identifiable sources of uncertainty should be reported
- All of these should be evaluated qualitatively

- Where uncertainty remains as to their qualitative impact on the assessment, these should be quantified to the extent necessary to provide sufficient reassurance to enable risk management decisions

The sources of uncertainty need to be identified in both the toxicology and the exposure assessment. An illustration of the application of such an approach can be found in EFSA (2007). All steps in the assessment should be considered systematically and evaluated qualitatively. One possible approach to this is to estimate the likely magnitude of uncertainty and direction of the impact of each source of uncertainty on the potential health outcome, using a subjective scoring system of pluses, and minuses, with a range as necessary (i.e. -, - -, - - -, +, ++, +++, and combinations of these). Similarly, the uncertainty in the overall evaluation is assigned a score or range of scores, based on subjective evaluation of the individual scores. It is often useful to include a tabular summary of the qualitative uncertainty analysis.

Sample table for qualitative uncertainty analysis. The symbols indicate whether a given uncertainty is such that the assessment is likely to over-conservative (+) or under-conservative (-). The relative magnitude of uncertainty is indicated by the number of symbols (e.g. +++ indicates much greater uncertainty that the true risk is likely to be lower than that with an uncertainty scoring +). Where the impact of the uncertainty is unclear, upper and lower estimates of the potential impact are provided (e.g. - -/++). Uncertainties with the greatest magnitude, i.e. - - - and +++, are those where efforts to refine the assessment further are likely to have the greatest impact.

Intake of [*insert name of relevant veterinary residue*] **Source of uncertainty**	**Subjective estimate of magnitude of uncertainty and direction of conservatism in outcome (e.g. +)**
Brief description of source of uncertainty	
Hazard identification	
Insert one row for each source of uncertainty	
(e.g. Toxicological relevance of critical endpoint)	
Hazard characterization	
Insert one row for each source of uncertainty	
(e.g. Confidence that NOAEL is adequate surrogate of NAEL)	
Exposure assessment	
Insert one row for each source of uncertainty	
(e.g. How realistic is estimate of consumption)	
Risk characterization	
Insert one row for each source of uncertainty	
(e.g. Have all relevant sub-populations been taken into account)	
Overall evaluation of uncertainty in the assessment *Short narrative text describing the subjective evaluation of the uncertainty in the overall assessment, based on the uncertainties identified above*	*Overall uncertainty* (e.g. - /++)

Where the overall evaluation of uncertainty does not provide sufficient confidence in the risk assessment, it might be possible to refine the assessment by quantifying one or more of the uncertainties with the greatest influence on the outcome, i.e. those scoring - - - or +++.

Quantitative evaluation of uncertainty can be undertaken using either deterministic or probabilistic approaches. The applicability of probabilistic approaches to residue evaluations by WHO/FAO has been considered previously, when it was concluded that data availability was such that these were not realistically feasible for the present time. In the deterministic approach, various assumptions are included in the analysis, for example all food contains residues at the MRL, only food based on use pattern contains residues, include or exclude equivocal endpoints.

The impact of these various alternative assumptions on the outcome is then determined. This results in a range of possible outcomes, which is then used in the assessment of the overall uncertainty in the assessment.

In general, an iterative evaluation of uncertainty is undertaken, in which progressively more of the uncertainties are quantified, until there is sufficient confidence in the overall outcome of the assessment.

4. Communication of the Risk Assessment

Specific consideration of Risk Communication depending on the different risk assessment tools (e.g application of MOE approach, or TTC) will be added in later versions of this document.

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Glossary

Acute Reference Dose (ARfD)
The ARfD of a chemical is the estimate of the amount of a substance in food or drinking water, expressed on a body weight basis, that can be ingested in a period of 24 h or less, without appreciable health risk to the consumer on the basis of all the known facts at the time of evaluation. It is expressed in milligrams of the chemical per kilogram of body weight.

Benchmark Dose (BMD)
A dose of a substance associated with a specified low incidence of risk, generally in the range of 1–10%, of a health effect; or the dose associated with a specified measure or change of a biological effect.

Benchmark Dose Lower Bound (BMDL)
95% lower confidence limit of the BMD.

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

Hazard
Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub) population is exposed to that agent.

Margin of exposure (MOE)
Ratio of the no-observed-adverse-effect level (NOAEL) or benchmark dose lower confidence limit (BMDL) for the critical effect to the theoretical, predicted, or estimated exposure dose or concentration.

Margin of safety (MOS)
For some experts the Margin of Safety has the same meaning as the Margin of Exposure, while for others, the Margin of Safety means the margin between the reference dose and the actual exposure dose or concentration.

Maximum residues levels for veterinary drugs (MRLVD)/Maximum residue level (MRL)
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 and estimated food intakes.

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

No-observable adverse effect level (NOAEL)

The 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 life span of the target organism under defined conditions of exposure.

Risk
The probability of an adverse effect in an organism, system or (sub) population caused under specified circumstances by exposure to an agent.