codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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Charleston, South Carolina, USA

DISCUSSION PAPER ON RISK ANALYSIS PRINCIPLES AND METHODOLOGIES IN THE CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

(Prepared by France)

Governments and international organizations wishing to submit comments on the following subject matter are invited to do so **no later than 1 October 2001** as follows: U.S. Codex Office, Food Safety and Inspection Service, US Department of Agriculture, Room 4861, South Building, 14th and Independence Avenue, S.W., Washington, DC 20250, USA (Fax No: +1.202.720.3157; e-mail: uscodex@usda.gov), with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, FAO, Viale delle Terme di Caracalla, 00100 Rome, Italy (Telefax: +39.06.5705.4593; E-mail: Codex@fao.org).

BACKGROUND

1. At its Ninth Session, which was held in 1995, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) approved the integration of a scientific risk analysis into its work and agreed that a document on this topic would be prepared by France with the help of Australia, Canada, the United States, Norway, New-Zealand and the Netherlands to be examined at its 10th Session (ALINORM 97/31, para.14). France prepared this document with the help of the United Kingdom, FAO and WHO. The comments made during the 10th Session of CCRVDF in 1996 and the two expert consultations organised since then by the FAO and WHO on risk management and risk communication were taken into account, which led to a new version presented during the 11th Session of CCRVDF in 1998 in Washington. As this text did not raise any particular objection during this session, the French Delegation was asked to make proposals intended for the 12th Session of CCRVDF regarding priority actions of the involvement of this committee in risk management.

2. The 12th Session of the CCRVDF agreed that a drafting group (Australia, Brazil, Canada, Chile, Japan, Mexico, the Netherlands, New Zealand, the Philippines, Sweden, Switzerland, Thailand, the United States, the Secretariat of JECFA, the European Community, OIE, WHO, Consumers International and IFAH) led by France and Poland would prepare a discussion paper for government comments well before the next Session of the Committee (ALINORM 01/31, paras. 15-20).

3. A first draft report has been mailed to all the members of this writing group in March 2001 for a 4 month consultation period. Comments have been received from Japan, Thailand, the United States, OIE, Consumers International and IFAH.

4. This report on risk analysis includes two annexes:

- Annex 1: establishment by CCRVDF of a risk assessment policy for the setting of maximal residue limits for veterinary drugs in foods
- Annex 2: Risk management and Codex procedures for establishing MRLs of veterinary drugs : recommendations to CCRVDF.

INTRODUCTION

5. Risk analysis is described in numerous Codex documents, CL 1995/40-CAC, ALINORM 93/37, ALINORM 95/9, CX/RVDF 94/5 and CX/EXEC 96/43/6, as well as the reports of the joint FAO/WHO consultations held in March 1995 (risk assessment), January 1997 (risk management), February 1997 (food consumption and assessment of the exposure to chemical substances) in February 1998 (risk communication). It consists of three components: risk assessment, risk management and risk communication. This report aims at determining to which extent these different components are taken into account in the Codex procedure for setting Maximum residue limits for veterinary medical products in foods. In the framework of risk analysis, the report sets out to determine the respective roles of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and CCRVDF. It then sets out to make a few proposals to further integrate the risk analysis procedure into the establishment of MRL and the functioning of JECFA and CCRVDF.

6. The definitions of the different risk analysis components which are mentioned in this report are those provisionally adopted by the Codex Alimentarius Commission in July 1997 and which are mentioned in the "definitions" section of the *Procedural Manual*.

7. The Codex Alimentarius Commission globally aims at setting standards intended to ensure the safety of foods. The veterinary use of chemical substances as veterinary medicinal products can affect the safety of food and consequently have an adverse effect on consumer health. Risk assessment is part of the general framework applicable to all the hazardous substances susceptible to contaminate foods independently of their origin. This assessment should lead to estimate, as globally as possible, the risk/benefit ratio for public health for the substances used as veterinary medicinal products. This should lead to the definition of acceptable daily intakes (ADI), the setting of maximum residue limits in foods from food-producing animals and the proposal of appropriate analytical methods to control the compliance with these food standards.

MANDATES OF CCRVDF AND JECFA

8. At its 16th Session which was held in 1985, the Codex Alimentarius Commission took account of the recommendation of the Joint FAO/WHO Expert Consultation on Residues of Veterinary Drugs in Foods which was held in 1984 and decided to create a Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). The Terms of Reference of CCRVDF are as follows:

- to determine priorities for the consideraton of residues of veterinary drugs in foods
- to recommend maximum levels of such substances
- to develop codes of practice as may be required
- to consider methods of sampling and analysis for the determination of veterinary drug residues in foods.

9. During its First Session in 1986, CCRVDF agreed with the following definition of veterinary drugs: "A veterinary drug means any substance applied or administered to any food-producing animal, such as meat or milk producing animals, poultry, fish or bees, whether used for therapeutic, prophylactic or diagnostic purposes or for modification of physiological functions or the behaviour."

10. JECFA, which is separate and independent from the Codex Alimentarius Commission give scientific advice to the Codex Alimentarius Commission, member countries of FAO and WHO and any other interested parties. It also helps CCRVDF to achieve its mission by evaluating the available scientific data regarding the metabolism, pharmacokinetics and toxicity of the substances used in veterinary medicine and their residues. When the outcome of this scientific assessment of JECFA becomes available, it will be made available to the session of CCRVDF scheduled after the relevant JECFA meeting and the Codex Secretariat

distributes proposed MRLs at Step 3 for comments.

RISK ANALYSIS

Risk Assessment

11. Risk assessment is a science-based process including four steps

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

12. 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.

Hazard Identification

13. The purpose of this step is to identify drug residues present in food of animal origin and capable of causing adverse health effects.

14. The definition for a veterinary drug residue adopted by the Codex Alimentarius Commission includes both the parent substance administered to an animal and all the chemical compounds resulting from the metabolic changes of this substance. The metabolic changes, which are ordinary followed using radiolabelled drugs, may vary in magnitude depending on the substances and, in some cases, be intense and rapid. In this case, it is technically and hence economically difficult to identify all the residues resulting from the parent substance. Therefore, in the case of intense metabolism of the studied substance, hazard identification is mainly limited in practice to the parent substance and to the main residues resulting from its metabolism while, for risk management purposes, most of the time, the total residue is considered a hasard. Consequently, while the MRL values are usually expressed in equivalent of the studied substance for practical reasons, the consequent calculations of consumer exposure consider the full range of residues of toxicological significance derived from the metabolism of the substance.

15. There are however two exceptions to this general rule:

- When the studied substance, associated with an adverse effect not relating to the digestive tract, generates bound residues, bioavailability studies make it possible to discount non-bioavailable compounds from the residues covered by the MRL.

- When the risk assessment of a particular substance is based on a clearly defined pharmacological adverse effect – and this is particularly the case if the studied substance is also used in human medicine- and when studies comparing the pharmacological activity of the parent substance and that of its main metabolites in an adequate model are available, the MRL established will only relate to the compounds expressing this pharmacological activity.

16. Once the adverse effects of the drug residues have been quantitatively assessed in the following hazard characterisation step, the toxic effects observed in the laboratory animal have to be extrapolated to humans. The question is whether the drug residues present in the foods from treated animals are likely to have the same toxic effects on the consumer as those observed in the laboratory animal to which the studied drug was administered. This can only be answered by comparing the metabolic profiles of the substance in the laboratory animal, where the adverse effect was identified, and in the food-producing animal which, when treated, will be the source of consumer exposure to drug residues. The comparability of these metabolic profiles provides the adequate scientific basis for extrapolating the results of the toxicological evaluation in the laboratory animal to humans. Such metabolic information is however incomplete for older drug and, in this case, very often extrapolation from animals to humans is thus based on assumption rather than on the analogy of metabolic profiles.

Hazard Characterisation

17. At this step, the nature of the adverse health effects associated with veterinary drug residues that may be present in food is assessed qualitatively and/or quantitatively. Completing this difficult task requires a methodology to evaluate the results of the different toxicological and pharmacological tests required. In 1987 WHO published a compendium "Environmental Health Criteria 70: Principles for the Safety Assessment of Food Additives and Contaminants in Food" describing the methodology used to evaluate the safety of contaminants present in foods and the list of toxicological tests to be performed.

18. Hazard characterization can sometimes be based on observations in humans. It is, however, mostly based on toxicological studies on laboratory animals. I*n vitro* experiments can also contribute to this characterization.

19. If epidemiological studies can be carried out in humans, then it would be possible to directly characterize an adverse effect caused in humans following the ingestion of toxic drug residues, without extrapolating from an animal experiment. Unfortunately, the difficulty of implementing these studies make them unlikely to be able to identify the adverse effects of low residue levels with the required efficiency. Revealing allergic effects in humans from penicillin residues is a fortunate exception. More frequently, useful information can be obtained for drug classes that are also used in human medicine. In this case it is possible to observe adverse effects caused by high doses used when treating humans, but it is still necessary to extrapolate to the risks associated with the continuous ingestion of small doses of residues. The tests carried out on humans using drugs that are also employed in veterinary medicine can provide indications on doses associated with pharmacological effects. The difficulty, however, lies in the fact that the purpose of these tests peculiar to human medicine is to determine an optimal efficient dose and not a dose without effect or the effects of low doses for extended times including life time, which is the whole point of evaluating the safety of veterinary drug residues.

20. As public opinion is increasingly turning against animal experiments, scientific research has sought for a few years to develop *in vitro* testing which may replace animal experiments. However, despite the progress made, the results are, in most cases, rarely comparable to the corresponding *in vivo* tests because of the simplification of their protocols and lack the interaction of many complex systems over time. However, they do provide valuable complementary information to improve the qualitative characterization of hazards.

21. Consequently, the shortcomings of studies conducted *in vitro* and on humans make animal experiments the best source for the toxicological and pharmacological information needed to evaluate the safety of veterinary drug residues. JECFA uses a very complete series of toxicological tests, most of them codified by OECD protocols, to detect general or specific toxic effects. This series combines acute, sub-acute or chronic toxicity tests and the detection of toxic effects on reproduction, and teratogenic, mutagenic, carcinogenic and immunotoxic effects. The undesirable effects sought also include the pharmacological effects that might help characterize the hazards for residues of certain substances such as, for exemple antibiotics, hormones, ßagonists, tranquillizers and anti-inflammatory substances.

22. For economic and ethical reasons (to spare animal life), this complex series of toxicological tests is most often restricted to the parent substance and is not used to assess the toxicity of the residues resulting from the metabolism of this substance. Therefore, the lack of knowledge of the specific toxic potential of metabolites leads to the assumption that the parent substance and all its metabolites are jointly responsible for the toxic effects observed in animals and that the toxicity of each metabolite is identical to that of the parent substance except in the case of evidence to the contrary.

23. In each toxicological test, laboratory animals are exposed to increasing doses of the studied substance, calculated to cause adverse effects to emerge, if any. Identifying the correlation between the doses administered and the effects observed is an important component of hazard characterization. The objective 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 on experiment animals. This is defined as the dose-response relationship. The joint FAO/WHO expert consultation of March 1995 estimated that setting the ADI, the quantity of residues that can be ingested daily over a lifetime by the consumer without

appreciable health risk, was the final stage of this hazard characterization step. It should therefore be inferred that, as far as veterinary drug residues are concerned, this step concerns both :

- the dose-response relationship that must be established for the laboratory animal undergoing toxicological tests and that helps determine a no observed effect level (NOEL) in the animal

- extrapolating to humans the conclusions of this toxicological test on the laboratory animal to set an ADI.

24. In its dose-response assessment to determine a dose that is risk free for human health, JECFA has never used mathematical models to extrapolate risks to low doses and determine a so-called "virtually safe" dose, on the grounds they have not yet been validated and can lead to very different conclusions from identical experimental data. However, JECFA could usefully address this matter in its deliberations. When the progress made in this area makes it possible to choose between various validated models, this exercise will no longer be solely associated with risk assessment but will also incorporate a component of risk management. While the scientific approach of risk assessment is best suited to determine the choice of mathematical tool adapted to the mechanism leading to the toxic effect to be modelled, any decision regarding the virtually safe dose associated with the concept of socially acceptable level of risk for the frequency of adverse effects to consumer health, which can be of 1/10 000, 1/100 000, 1/1 000 000 or 1/10 000 000, should clearly come under the responsibilities of risk managers.

25. The safety factor procedure used by the JECFA is more pragmatic than the low dose extrapolation procedure discussed above. It is based on determining a NOEL for the laboratory animal and a subsequent ADI for humans resulting from this NOEL by applying a safety factor. A NOEL is, by definition, the highest dose in a toxicological test that caused no adverse effect in the laboratory animal.

26. The value of the safety factor used to calculate an ADI from a NOEL is normally 100. It comprises two factors of 10 :

- The first is designed to:

    - offset the uncertainty of the NOEL value that arises from the necessarily restricted number of animals used in the toxicological study
    - take into account the possibility that human beings might be more sensitive to the toxic effects than the most sensitive laboratory animal. This concept is not based on any scientific evidence but is used as a conservation for the uncertainties inherent in the process of risk assessment.
    - If the NOEL has been determined on the basis of undesirable effects on humans, this factor is not used.

- The second factor is designed to take account of the genetic variability of the consumers susceptible to eat these drug residues, which is much wider than the genetic variability of the laboratory animals used in the toxicological study. With regard to the second factor, it should not be omitted that some human sub populations (very young, very old, pregnant women, people with illness or with unique metabolic conditions) may be more than 10 fold more sensitive than the average healthy adult. On the other hand, there are other safety factors associated with the exposure assessment (cf para. 413) which provide additional protection of public health..

27. This safety factor value of 100 can be increased to take account of the severity of the toxic effect observed, or to offset shortcomings in the toxicological study considered or the whole toxicological dossier supplied. A NOEL is therefore calculated for each toxicological study and the ADI with the lowest value will be finally adopted for the studied substance provided the end point is considered toxicologically valid for human and is not contradicted by other information on the toxicity mechanism.

28. When the JECFA has not been provided with all the needed information, it can nevertheless propose a temporary ADI if the lacking information is not likely to change significantly the outcome of the risk assessment. In this case, as a precaution, an additional safety factor of 2 is used for calculating this temporary ADI.

29. This procedure for determining ADI is based on the assumption that humans are at least as sensitive as the most sensitive laboratory animal exposed to the most sensitive test. This concept, which relies on no scientific evidence, is for compensating, as a matter of caution, the uncertainties associated with this risk assessment approach.

30. This approach has, however, two drawbacks: one is related to the need to have a NOEL; and the other to the standard characteristic of the safety factor.

31. If, for any reason, it is not possible to determine a NOEL for an animal then it is not possible to establish an ADI. Nevertheless, if it is possible to set MRLs for a substance, (ex : Carbadox) on the basis of the available metabolic and residues depletion studies. In such a case, the approach chosen, which is related to risk management, will be pragmatic and prudent.

32. The safety factor value of 100 which is often used does not consider the shape of the slope of the toxicological dose-response curve. Extrapolation from animals to humans does not therefore always guarantee the same margin of safety.

Exposure Assessment

33. Consumer exposure to residues mainly results from the ingestion of these contaminants through foods.

34. Estimating consumer exposure is based on the daily consumption of foods combined with the amount of veterinary drug residues in the food.

35. In view of the difficulty of assessing such exposure from a rigorous approach, JECFA preferred, for purposes of simplification, not to spend time and money for expensive surveys on residues ingested but to reduce the risk to the consumer to the absolute minimum by deliberately overestimating exposure. This overestimation results from the combination of the worst-case scenario and the concern to use only one representation and to globally standardize consumer food intake.

36. The worst-case scenario is based on the assumption that all the foods originating from animals likely to be treated with a drug is always contaminated by the marker residue determined for this drug at a level equal to the value of the MRLs set in these foods.

37. The above scenario is not an accurate reflection of reality, at least for the following reasons:

- by definition, veterinary medicinal products are intended to cure ill animals and thus only some animals require a veterinary therapy
- if an animal or a group of animals require a veterinary therapy, a medicinal product or a combination of a few veterinary medicinal products will be used. The use of a medicinal product at a given time consequently excludes the use of other products and the consumer will only be exposed to the residues of the substance or of a limited number of substances used and not to the residues of all the other pharmacologically active substances available in the veterinary therapeutic collection.
- a number of diseases affect young animals and, in this case, administering veterinary medicinal products long before the slaughtering of these animals does not produce residues susceptible to pose a public health problem.
- many veterinary medicinal products are used for curing purposes for the treatment of individual animals. The probability for a consumer to be exposed to residues of this type of treatment is thus limited
- the use of certain products, in particular antiparasitic substances, is seasonal and the potential exposure of the consumer to residues of these substances is not continuous.

38. Lastly, statistical methods for establishing withdrawal time used by the national authorities responsible for licensing veterinary drugs strengthen the highly protective character of this scenario in relation to public health.

39. The effort to standardize the daily food intake at the international level led to adopt the following

intakes: 300 g muscle, 100 g liver, 50g kidney, 50 g fat, 100 g egg, 1.5 l milk and 20g honey. The value set for milk seems to be particularly high but it was estimated that this value was appropriate to ensure that infants and young children do not take veterinary drug residues at doses higher than the acceptable daily intakes established. This daily intake obviously represents an excessive estimate of the real consumption but JECFA estimated that the potential error resulting from the use of these intake values represented only a minor part of uncertainty inherent to the risk assessment procedure and constituted a supplementary safety factor for public health protection.

Risk Characterization

40. The last step of the general risk assessment approach sets out to provide a qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.

41. Risk characterization for public exposed to drug residues present in food represents a particular case insofar as:

- the administration of veterinary medicinal products to animals is subjected to well controlled conditions defined by marketing authorisations
- the values of the MRLs for a veterinary drug are established so that the theoretical maximal daily intake of its residues is lower than the corresponding acceptable daily intake
- the compliance with these MRLs is guaranteed by the compliance with the withdrawal periods prescribed for each veterinary medicinal product.
- the analytical methods are made available for surveillance monitoring purposes

42. As estimated by the 1995 joint FAO/WHO expert consultation in a study on the implementation of the risk analysis concept in the assessment of drug residues, the risk characterization step should lead to the establishment of MRLs.

43. Thus, since

- the ADI established determines the acceptable maximal values for the theoretical daily intakes of residues
- the MRLs correspond to the acceptable maximum residue levels in the various foods of animal origin which make it possible to comply with these ADI given the established standardized food consumption this risk characterization step rather corresponds to an establishment of food standards, i.e. MRLs, which make it possible to guarantee that the insignificant risk for public health which was accepted when acceptable daily intakes were established, will be maintained at a very low level, than to an estimate of the risk for public health.

44. JECFA does not use rigorous mathematical models to derive MRLs from an ADI. MRLs are set, using available metabolism and pharmacokinetic data, at the end of a procedure where pragmatism is most important and risk management has a major influence. The few examples below illustrate the close interaction between risk assessment and risk management in setting MRLs.

- The MRLs express a maximum threshhold which the marker residue of a drug likely to pose a risk to consumer health must not exceed. Since, as part of monitoring plans, it is impossible to analytically measure a series of residues with widely differing chemical structures, control requirements compel that MRL values be expressed in terms of a single chemical entity, known as the marker residue. For a substance to be eligible as a marker residue, it is important that the information be made available on the marker residue concentration in the different tissues of treated animals along with the total residues, as it has to reflect them. In practice, these studies which require using labelled substances are difficult and expensive. Data available on this topic being thus often limited, the values of the concentration ratios between marker residues and all the residues to be taken into account are not very precise and are not necessarily established for all tissues. Moreover, for obvious practical reasons, this marker residue must also satisfy two requisites: it must permit the development of a practical dose assay and a chemical

standard for the purposes of official controls. The parent substance is consequently often chosen as marker residue.

- The MRL values for the different tissues (muscle, liver, kidney, fat) are set in proportions that reflect the tissue distribution of the residues. However, to avoid producing a set of highly complex figures for the different tissues and the different animal species, JECFA tries to harmonise MRL values among animal species as far as possible to keep their number down. This approach is all the more legitimate since it is not easy to explain to the public opinion that the MRLs for the same tissue, muscle for example, can be different between cattle, pigs, goats and poultry and that a consumer will ingest different amounts of drug residues, at least theoretically, when the same amount of meat from these different animal species is eaten. In addition, the JECFA has established identical MRLs for 31 of the 41 substances intended to various animal species. Therefore it appears necessary to verify whether it was appropriate for the other ten substances to establish different MRL values for the different animal species, and wether it is really useful for the protection of public health to continue to establish MRLs for identified animal species that requires supplying information on the metabolism and the kinetics of tissue residues for each of these animal species. Moreover, this current approach, which limits the proposals of MRLs to the animal species for which data are available, does not make it possible to establish MRLs for the so-called minor species which represent a too limited economic market for the veterinary pharmaceutical industry which does not want to finance the necessary studies.

- When it appears that the residue content in a given tissue is likely to be too small for a feasible control after the recommended withdrawal time determined by residue contents in other tissues has elapsed, JECFA may consider it useful to propose no MRL for that particular tissue. However, for a tissue such as muscle or liver that may be in international commerce, a MRL may be needed to demonstrate safety to the authorities of the importating countries

- When a veterinary drug is intended for animals producing meat, milk and eggs, the assignment of the acceptable daily intake of residues established from the ADI between these various foods is obtained from a pragmatic approach.

- When a substance is used both as a veterinary medicinal product and as a pesticide, the amount of residues ingested originating from the consumption of treated plants, is deduced from the ADI in order to determine the maximum amount of residues originating from animal-derived foods which can be ingested daily by the consumer without risk to their health.

- Even though JECFA is not involved in setting withdrawal times, it has to refer to a practical withdrawal time in order to establish a consistent set of MRL values. If it appears that compliance with the MRLs requires unrealistically long withdrawal times, no MRL may be recommended. This situation may arise in particular for milk and eggs.

- The concern to recommend withdrawal times compatible with good animal husbandry practices can also lead to the "use" of a variable percentage of established ADI depending on the depletion rate of residues. Thus, when a substance disappears rapidly from the body of treated animals, a practicable withdrawal time which guarantees public health protection can lead to a theoretical daily intake of 10 % of the ADI, whereas the same approach will lead to a theoretical intake which can correspond to the total ADI when the substance disappears more slowly.

- The MRL values may be reduced to take account the normal conditions under which a particular veterinary drug is used in animal husbandry if these lower MRL values can be controlled by a practical analytical method.

45. The whole pragmatic approach used to establish MRLs indicates a strong interlinkage between risk assessment and risk management in this area. The particular relevance of scientific data from pharmacokinetics, metabolism and statistics suggests that JECFA should retain its role regarding the proposal of MRLs to CCRVDF. However, CCRVDF is basically involved in risk management and, as such, should also assume greater responsibility in this connection when invited to consider MRLs proposed by JECFA that have been based on the choices made by this expert committee in terms of risk management.

Risk Management

46. Risk management is understood as the process, distinct from risk assessment, of weighing policy alternatives considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.

47. The joint FAO/WHO expert consultation that discussed this issue in January 1997 tried to structure the content of this concept of risk management, but its conclusions were somewhat imprecise and further thought is needed on defining the components of risk management. The consultation divided risk management into four components, i.e. risk evaluation, assessment of management options, implementation of management options and monitoring and review. This report is limited to the first two components of the risk management stage as far as the other two come more particularly under the responsibility of member states, even though CCRVDF adopted a text making proposals in the area of residue surveillance. (Guideline for the establishment of a regulatory programme for control of veterinary drug residus in food) and is considering another one focusing on the control of veterinary drug residus in milk and milk products.

Risk Evaluation

48. This first stage of risk management includes :

- identification of a food safety problem
- establishment of a risk profile
- ranking of the hazard for risk assessment and management priority
- establishment of a risk assessment policy for conduct of risk assessment
- commissioning of risk assessment
- consideration of risk assessment result.

49. The first three components of this risk management correspond to the work currently done by CCRVDF with the help of member states during the fist step of the Codex MRL establishment procedure. On that occasion, CCRVDF establishes lists of priority substances likely to pose a public health problem and transmits them to the JECFA secretariat so that the WHO and FAO experts of JECFA carry out an assessment of the risks related to these substances (step 2 of the Codex procedure). It seems desirable that CCRVDF considers the procedure for establishing these lists of priority substances which will be evaluated by JECFA because the general criteria adopted in 1986 which make it possible to establish them are less transparent than before. It would be necessary to check whether the modifications adopted in 1994 are applicable or not.

50. The establishment of a risk assessment policy is a central element of risk management which would deserve major thought. The 1997 FAO/WHO consultation estimated that this policy should be intended to protect the scientific integrity, coherence and transparency of risk assessment.

51. The requirements of the protection of scientific integrity, coherence and transparency of the risk assessment carried out by JECFA must absolutely be met so that the trust in the work and the MRL proposals made by JECFA is total. Since JECFA is a structure managed by FAO and WHO, a discussion should be started between CCRVDF and these two international organisations to reach this objective of risk management. It should particularly focus on the management of JECFA meetings by FAO and WHO .

52. Determining safety factors should be a priority topic because it is particularly important for public health protection. Setting MRLs is in fact based on a series of conservative assumptions which constitute safety factors, such as:

- the assumption that humans are at least as sensitive as the most sensitive laboratory animal to a potentially toxic residue which explains the use of a safety factor to infer an ADI from an NOEL, which is usually 100. It can include a supplementary safety factor of usually 2 to establish a provisional ADI until the complementary data necessary to convert it into a final ADI are obtained.
- the over-estimate of consumer exposure to drug residues;

- the assumption that the total residues covered by the MRLs are considered to be as toxic as the parent substance (When a metabolite is proved to be more toxic than the parent substance, the MRL is expressed as a function of this metabolite.)
- the assumption of total bioavailability of the so-called free residues from the human gastro-intestinal tract

53. Establishing the value of these different safety factors seems to be one of the basic components of public health policy . This risk needs to be assessed in the light of the nature of the observed toxic effects, the quality of data supplied on residue toxicity and contents, the benefit-risk ratio the assessment of which depends on the therapeutic or zootechnical purpose of the studied substance. This is a central aspect of risk management that should be dealt with by the mandated parties. It is odd that CCRVDF has never addressed this important matter and issued the necessary guidance to JECFA.

54. Another example can be taken in the area of technical guidelines. JECFA had to establish such guidelines to guide its evaluations and ensure the coherence of these evaluations. It is necessary to use the scientific skills of JECFA to provide consistent and scientifically supportable recommandations to the CCRVDF. It would also be desirable that CCRVDF assess these guidelines more critically than currently done in order to adopt them before they are used as reference by JECFA..

Assessment of Management Options

55. The joint FAO/WHO consultation divided this step into three parts: identification of available management options, selection of preferred option, including consideration of an appropriate safety standard, and final decision. Up to now, CCRVDF has put very little effort in this area as far as JECFA suggests only one MRL for each substance and each tissue or food. When a discussion is started on this topic on the initiative of a delegation, it mostly concerns the difference between the MRL values suggested by JECFA and those adopted in the country or region of the concerned delegation. CCRVDF seldom considers various possible options, such as the allocation of the ADI between various tissues, milk and eggs or between plant- and animal-derived foods when the substance can be used both as a veterinary medicinal product and as a pesticide. JECFA has already declined to recommandations on the use of certain veterinary medicinal products for dairy cows and laying hens as well as for pigs (tranquillisers) when the withdrawal times necessary to comply with the established MRLs seemed too unrealistic given the usual conditions of use of veterinary medicinal products. CCRVDF only rarely addresses this matter on its own initiative.

56. The joint FAO/WHO consultation on risk management has insisted that decisions on acceptable levels of risk should be based on considerations of public health. It has also accepted that other considerations be taken into account where these could be objectively determined. The 12th CCRVDF agreed that the following list of the other legitimate factors have been taken into account in the framework of risk analysis for the establishment of MRLs for veterinary medicinal products : Good Practices in the Use of Veterinary Drugs, Good Manufacturing Practices for veterinary drugs, technical feasibility, substantial changes in food composition and quality characteristics, the need to minimize exposure to residues, the ALARA (As Low As Reasonably Achievable) concept, food consumption estimates and residues from other sources than animal products. CCRVDF in connection with the ongoing work of the Codex Committee on General Principles will give further consideration as to which other legitimate factors could also taken into account for establishing MRLs for veterinary drugs.

Implementation of Management and Monitoring Options

57. These last two components of risk management are essentially under Member State responsibility. However CCRVDF advises States on the extent of validation undergone by analytical methods to be used for controlling the compliance with MRLs.

Risk Communication

58. A more recent joint FAO/WHO consultation in February 1998 sought to define this third component of risk analysis which was described in 1995 as an interactive exchange of information and opinion on risks among officials responsible for risk assessment and management, consumers and other interested parties.

Although examination of this very complex subject is recent and needs further reflection, there would appear to be many parties potentially involved in such communication and the structures responsible for risk assessment and management have a duty to report on their respective areas of competence. This report will be limited to the involvement of JECFA and CCRVDF in this area

Role of JECFA

59. JECFA provides satisfactory technical communication through

- summary reports of the meetings which are rapidly available
- detailed reports of the meetings which are published later
- WHO and FAO monographs dealing with the assessment of toxicological data and studies of residues, respectively.
- the publishing of the scientific data to be provided to assess the safety of veterinary drug residues

60. It would be nevertheless useful if JECFA could better inform CCRVDF by clearly indicating in the assessment reports of each substance

- the choices made during the risk assessment process that relate to risk management
- the scientific uncertainties met, the degree of confidence in the data provided and how they were taken into account in risk assessment

61. The official publication of these technical texts by FAO and WHO is obviously a difficult time-consuming exercise given the limited human resources. The deadlines for the publication of the detailed reports of the JECFA meetings and WHO and FAO monographs are too long. They hamper the good functioning of CCRVDF because the delegations do not receive in due time the information/data necessary to conduct a critical evaluation of the ADI and MRL proposals made by JECFA. They consequently adopt JECFA proposals without debate, which does not represent any added value to the work already done, or, on the contrary, they express their disagreement and bring the procedure at a standstill. This situation should rapidly be improved.

Role of CCRVDF

62. The involvement of CCRVDF in communication on risk management is extremely restricted. It is limited to meeting reports, which, for financial reasons, are increasingly shorter so that they no longer constitute efficient communication media. Moreover, it should be noted that the Codex procedure for establishing MRLs only takes into account substances for which JECFA could propose either numerical or non specified ADI and MRLs. The other substances are withdrawn from the procedure whatever the reasons why no ADI and MRLs were proposed (high toxicity, insufficient quality of the dossiers) and no pertinent information is given on the reasons which led to withdraw them from the Codex procedure. This should also be improved.

CONCLUSIONS

63. This report shows that the procedure for setting veterinary drug MRLs incorporates the concept of risk analysis. The separation of responsibilities in terms of risk assessment and risk management is a reality since risk assessment is entrusted to JECFA and risk management to CCRVDF. Nevertheless, it has to be recognised that this separation is far from being complete. As a matter of fact, it is obvious that the priority of the Codex management of the establishement of MRLs of veterinary drugs is to limit as far as possible the presence of drug residues in foods of animal origin so that the resulting risk to public health can be considered as negligible. Consequently, the areas covered by risk assessment and management are not totally separate and various criteria relating to risk management strongly influence the scientific approach of the JECFA in its risk assessment, leading to the establishment of MRLs.

64. Scientific experts of JECFA thus had to establish a risk assessment policy which made it possible to ensure the consistency of the assessments carried out by this committee in a transparent manner without involving CCRVDF, even though is the committee in charge of risk management in the Codex procedure,

into the critical consideration of this strategy.

65. It is essential that CCRVDF starts some thought to increase rapidly the involvement of this committee, which is made up of national delegations, in the risk management component of this risk analysis approach. Among the actions to be considered for establishing a risk assessment policy, which defines the concept of socially acceptable risks, the choice of the safety factors to compensate for the uncertainties inherent to this assessment and of the methodological approaches to be used in risk assessment should be a priority initiative.

ANNEX I

ESTABLISHMENT BY CCRVDF OF A RISK ASSESSMENT POLICY FOR THE SETTING OF MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS IN FOODS

1. INTRODUCTION

1. The establishment of a risk assessment policy is one of the components of risk evaluation, which is entirely part of risk management according to the structure of the risk analysis approach as defined by Codex Alimentarius Commission. Establishing such policy is the responsibility of risk managers, even though it is desirable that this work benefits from the competence of the scientists in charge of performing risk assessment.

2. A risk assessment policy aims at supplying a frame and clear guidelines intended for experts who have to perform a risk assessment in order to guarantee the objectivity, the consistency and the transparency of their assessment. This policy also aims at describing the general principles which make it possible to ensure the best public health protection against drug residues likely to be present in foods of animal origin.

3. This text, while supplying a frame for risk assessment , currently includes a list of questions intended for JECFA to clarify a number of topics. It has to be considered as the beginning of a dynamic. Moreover, although it does not intend to deal with the detailed methods of risk assessment, the content of this text will have to evolve to take account of new scientific knowledge and the experience gained through the work done.

Information requested from JECFA

4. Due to the similarities existing between the purposes justifying the establishing MRLs for veterinary drugs and pesticides, JECFA is requested to take into consideration the procedure followed for establishing MRLs for pesticides in order to avoid unnecessary differences between the two approaches

2. RISK ASSESSMENT

5. Codex Alimentarius Commission has defined risk assessment as a science-based process including four steps

- hazard identification
- hazard characterisation
- exposure assessment
- risk characterisation

6. The purpose of this process in this particular area of public health is to evaluate the known or potential adverse health effects on consumers resulting from exposure to veterinary drug residues.

2.1.Hazard identification

7. The purpose of this step is to identify drug residues present in animal-derived food and capable of causing adverse effects on consumer health.

2.1.1. Residues to be identified

8. The residues originating from the metabolism of a drug substance have to be identified in all the animal species likely to be treated by this substance. Although metabolite studies, which have to be performed using radio-labelled substances, carried out in urine and faeces, can supply useful information, they must be performed in all tissues (muscle, fat, liver, kidney) and edible products (milk, eggs, honey) originating from animal species treated with the considered substance.

Information requested from JECFA

9. JECFA is requested to indicate to CCRVDF:

- its requirements regarding the identification and characterisation of residues originating from a metabolised parent substance. Beyond the identification of the parent substance, can this study be limited to major metabolites, in particular when the parent substance is highly metabolised, or should it also include the metabolites which are present in smaller quantities? Could the concept of a minimum threshold, which would lead to require the identification of a metabolite only when its level is higher than a given percentage (5 or 10%) of total radioactivity, be accepted ? Can the study be limited to free residues or should bound residues be included ?
- whether it is possible to extrapolate metabolic data established for a food-producing animal species to another one and, if yes, the conditions required to perform this extrapolation as well as the limits to be set for this exercise.

2.1.2. Comparison of metabolisms between laboratory animals and food animals

10. In the area of drug residues, public health protection is ensured by setting acceptable daily intakes (ADI) which are derived from doses without observed toxic effect (NOEL) established from the results of toxicity trials performed on animals. To justify the validity of this extrapolation from animals to man, it is necessary to ensure that the residues/metabolites produced in the body of animals subjected to toxicity trials and which are responsible for the toxic effects observed are the same as those present in foods originating from treated animals to which the consumer is exposed. Studies necessarily have to establish that the metabolism of the substances studied are similar between the animal species subjected to laboratory tests that is the basis for establishing the ADI and all the animal species intended for human consumption.

Information requested from JECFA

11. For the reasons mentioned in paragraph 1., CCRVDF requests JECFA to indicate, based on its experience, whether the metabolic profiles supplied in the dossiers submitted for examination concern

- all the laboratory animals subjected to toxicity tests or only some of them (rodents for example)
- only the animal species from which the NOEL and the ADI are established
- all the food animal species, which can be a source of potential exposure of the consumer to drug residues
- only all major metabolites (those contibuting more than 10 % of the total residues in the food animal)
- the determination of the presence of bound residues

12. CCRVDF requests also JECFA to indicate what should be the strategy to be considered when a major metabolite in the edible tissues of a food animal is not suitably represented in the laboratory animal species that is the basis for the ADI.

13. Should the answers to the three previous questions be not clearly affirmative, JECFA is requested to specify the minimum requirements to be followed whether they are currently its own or those it would recommend in order to validate the extrapolation of the conclusions drawn from the toxicity trials carried out in laboratory animals to man.

2.2. Hazard characterisation

14. Hazard characterisation is a step of risk assessment which aims at qualitatively and/or quantitatively evaluating the nature of the adverse health effects associated with residues of veterinary drugs. This step concerns both :

- the dose-response relationship, which, when established for the laboratory animal undergoing toxicity tests, helps to determine a NOEL in the animal
- extrapolating to humans the conclusions of this toxicity test carried out on the laboratory animal to set an ADI.

2.2.1. Toxicity and pharmacology tests

15. As far the establishment of ADI and MRL aims at protecting public health against any residue level susceptible to damage consumer health, it is necessary that the dossiers submitted to JECFA contain the results of all the pharmacological and toxicity trials required, in particular in the "Environmental Health Criteria 70: Principles for the Safety Assessment of Food Additives and Contaminants in Food" compendium published by WHO in 1987. As the reliability of the results directly depends on that of the experimental protocols used, it is essential that these pharmacological and toxicity trials are performed in agreement with good laboratory practices.

Information requested from JECFA

16. The JECFA is requested to

- indicate to CCRVDF whether the list of pharmacological and toxicity tests published in the "Environmental Health 70" compendium published in 1987 is still entirely valid today or whether it is useful to update it.
- to suggest to the CCRVDF an appropriate methodology to assess the safety of residues of drug substances which have been marketed for numerous years and for which all the toxicity and pharmacology data required are not always available.
- to specify the experimental protocols to be implemented to assess, when applicable, the allergenic potential of a substance as well as the approach to be followed to establish a NOEL
- to present a report to CCRVDF on the methodology chosen to assess the possible selection by antimicrobial residues of resistant bacteria in the human gut flora, which guarantees the legitimacy of the approach followed and the validity of the experimental tests used.
- to present a strategy to assess the safety of residues of substances likely to cause acute toxic effects
- to present a report to CCRVDF on the current possibilities, or those which can be contemplated in the short or middle term, of using protocols of toxicity or in vitro pharmacology trials, which could be a valid alternative to animal experiments in order to meet the expectations of modern society anxious to reduce the use of animal experiments.

2.2.2. Residues to be tested

17. Should toxicity studies show that administering a substance to a laboratory animal leads to adverse health effects, it would be optimal to know whether these effects are produced by the parent substance administered or by one or several of its metabolites. CCRVDF has noticed that the study of toxicity effects is most of the time limited to the parent substance for technical and economic reasons. The approach currently followed by JECFA consequently means that

- the adverse effects observed in laboratory animals are considered as being the result of potential effects produced by the parent substance administered and its metabolites
- the metabolites have the same potential toxicity as the parent substance they derive from
- the residues, which have been shown through toxicity and pharmacology studies unable to produce adverse health effects and to have no toxic potential due to their low availability, can be discarded from this set of total residues a priori considered as a risk for public health

Information requested from JECFA

18. The JECFA is requested to indicate to CCRVDF whether

- the current technical requirements for assessing the safety of residues limit the toxicity studies requested to the parent substance only
- if no, the conditions which make complementary toxicity studies necessary for metabolites originating from the transformation of the parent substance
- the interest of studies on the relationships between the structure and the potential toxicity of the metabolites of a given substance in order to specify which total residues should be associated with the adverse effects observed in animals after the administration of the parent substance.

- the degree of harmonisation between the methods followed in this area by JECFA and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) which is in charge of the assessment of pesticide residues.

2.2.3. Establishment of a NOEL

19. Each toxicity or pharmacology trial should lead to determine a NOEL, which is defined as the highest dose having no observable adverse effect in the laboratory animal considered.

20. Determining adequate NOEL requires that particular attention be paid to the biological mechanisms leading to the appearance of toxicological or pharmacological effects in laboratory animals in order to ensure that the substance which caused this effect observed in animals is also a hazard for man and, consequently, that the NOEL established from this effect constitutes an appropriate basis for calculating an ADI for humans.

2.2.4. Establishment of an ADI

21. The ADI established for a substance is that with the lowest value, and thus the most protective against public health, which is deduced from a NOEL to which a safety factor is applied.
The value of the safety factor which makes it possible to deduce an ADI from a NOEL is usually 100. This value is divided into two factors with a value of 10 each.

22. The first factor is intended to:

- compensate for an uncertainty of the NOEL value resulting from the necessarily limited number of animals involved in the toxicity study concerned.
- take account of a possibly higher sensitivity of humans to the toxic effect observed than that of the most sensitive laboratory animal. If the NOEL is established from adverse effects observed in humans, this first safety factor is not used.

23. The second factor is intended to take account for a series of intraspecies variability factor (genetic variability, age, sex, health status…) of consumers who are likely to ingest drug residues, which is higher than that of laboratory animals involved in the toxicity study considered.

24. This value of 100 can be increased, if necessary, to take account of the seriousness of the toxic effect observed, from which the NOEL was established. It can also be increased to compensate for inadequacies in the toxicity study considered or in the whole toxicity dossier supplied.

25. It is recommended that a supplementary safety factor of 2 is taken into account when available data do not make it possible to establish a definitive ADI. The proposal for such temporary ADI involves the simultaneous request for supplementary information to be supplied within a given time limit to complete the assessment of the safety of the residues of the substance concerned. If the supplementary information is not available at the expiry date or if it does not make it possible to complete the assessment, the temporary ADI adopted is withdrawn.

Information requested from JECFA

26. Since the value of the safety factor chosen to calculate an ADI from a NOEL is a major component of the approach intended to ensure public health protection against veterinary drug residues, the JECFA is requested to inform CCRVDF about

- the criteria used to determine the values of the safety factors chosen to establish ADI.
- the possibility of using mathematical models for extrapolating effects at low levels in order to determine virtually safe doses for consumer health within a possible range from 1/10 000 to 1/10 000 000 depending on the toxicological pharmacologic end point issue, and, if necessary, the advantages and limits of this approach compared to the system currently implemented which uses safety factors. Definition of virtually safe dose and negligible risk should be elaborated.

- the methods used to round off ADI values when the calculation of this ADI from the NOEL and the safety factor chosen makes it necessary.

2.3. Exposure assessment

27. This part of risk assessment aims at quantitatively evaluating the likely intake of veterinary drug residues by the consumer via foods of animal origin consisting of muscle, liver, kidney, fat, eggs, milk and honey.

28. The estimation of this consumer exposure results from the association of daily food consumption and the level of residues in this food.

2.3.1. Estimation of the daily food consumption

29. The objective of JECFA and Codex Alimentarius regarding veterinary drug residues in food is to:

- guarantee, in this area, an equivalent public health protection in the various countries of the world by establishing a sole ADI for each substance
- favor international trade of foods of animal origin by establishing a sole MRL and a marker residue to monitor drug residues for each drug product in the principle edible tissues.

30. It is therefore necessary to consider harmonised daily intakes of animal-derived foods in order to calculate the MRL values from those of ADI. The values currently chosen are the following: 300 g for muscle, 100 g for liver, 50 g for kidney, 50 g for fat, 100 g for eggs, 1.5l for milk and 20 g for honey.

31. CCRVDF recognises that these values represent a major overestimation compared to the daily food intakes observed in the various countries. This overestimation, which is accepted in order to allow in a practical and economical way the international harmonisation in this area, is consequently a major supplementary safety factor.

32. For substances used both as veterinary medicinal products and pesticides, it is essential to take account of consumer exposure to residues also resulting from the ingestion of foods of plant origin likely to contain such contaminants.

33. The assessment of exposure of consumers to residues originating from the treatment of animals by a endogenous substance, such as hormones, raises a specific problem. Being naturally produced by the food producing animals, they are present as residue in the animal derived foods even in the absence of any treatment. In addition these substances are also produced by the organism of the humans. In assessing the safety of the residues of such substances during two different meetings (32th and 52th) the JECFA has followed two different approaches, even the outcome of the two assessments was the same. It would be appropriate that a risk assessment strategy be defined in this field.

34. As CCRVDF has identified a specific problem with the residues likely to be found at the injection site, it has discussed already several times a draft guideline aimed at proposing a strategy to adress this issue.

Information requested from JECFA

The JECFA is requested to

- compare the dietary models considered by JECFA and JMPR to establish MRL
- to transmit the results of this study to CCRVDF
- to indicate to CCRVDF, based on this study, whether it is necessary to modify the approach currently followed to calculate consumer exposure to veterinary drug residues
- to present to CCRVDF a study on the probability of ingestion by a consumer of meat of bovine, ovine or porcine origin containing an injection site and thus susceptible to be contaminated by a residue level higher than the MRL established. In its comments, the JECFA should also discuss the potential health effects of this unfrequent exposure and the need for acute NOELs, RFDs and ADIs.

- to present to CCRVDF a strategy to evaluate consumer exposure to residues originating from the treatment of an animal by a endogenous substance.

2.3.2. Estimation of the drug residue level in animal-derived foods ingested by the consumer

35. The calculation of consumer exposure to drug residues by JECFA is based on the assumption that any animal-derived food can contain at most, for each drug substance, the total residue levels determined by the value of the MRL established.

36. CCRVDF recognises that these assumptions lead to a major overestimation of dietary consumer exposure and thus to the establishment of a supplementary safety factor for the establishment of MRL as far as:

- veterinary medicinal products are intended to heal diseased animals. Thus, only some animals require the use of a veterinary therapy
- when an animal, or a group of animals, requires the use of a veterinary therapy, a medicinal product or a combination of a few veterinary medicinal products will be used. Consequently, the use of a very limited number of products at a given time excludes the use of all the other products and the consumer is potentially only exposed to the residues of these substances used and not to the residues of all the other pharmacologically active substances likely to be used in veterinary medicine.
- a number of diseases affect young animals and, in this case, the administration of veterinary medicinal products long before their slaughtering does not generate residues likely to raise a public health problem
- many veterinary medicinal products are used for healing purposes for individual treatments. The probability of a consumer to be exposed to residues of this type of treatment is limited.
- the use of certain drugs, in particular antiparasitic products, is seasonal. The potential exposure of the consumer to residues of these substances is thus not continuous.
- the withdrawal times established on the basis of a statistical approach for drug used for therapeutic and production purposes are very conservative.

Information requested from JECFA

37. The JECFA is requested to

- assess the overestimation of dietary consumer exposure to drug residues resulting from the consideration of the assumption used for this matter, corresponding to a worst-case scenario, by taking account of normal conditions of use of veterinary medicinal products and an estimate of the percent of the national herd that is likely to be treated at any one time and consumer consumption patterns
- perform an assessment of the exposure of infants to drug residues likely to be present in milk and, based on this study, identify whether a health problem may arise for them.

2.4. Risk characterisation

38. Given the uncertainties inherent to risk assessment, the last step of the general approach of this assessment aims at qualitatively and/or quantitatively estimating the probability of the occurence and the severity of adverse health effects in a given population based on hazard identification, hazard characterisation and exposure assessment.

39. According to the analysis performed on this topic by the joint FAO/WHO consultation in 1995, the risk characterisation step pertaining to veterinary drug residues leads to the establishment of MRL.

40. As far as

- the administration of veterinary medicinal products to animals is subjected to well controlled conditions defined by marketing authorisations

- ADI determine the maximal amounts of residues which can be ingested daily for lifetime by the consumer without appreciable risk for his health
- the MRL values are established so that the theoretical maximum daily intake of total residues is equal or lower than the level determined the corresponding ADI.

41. The objective of this risk characterisation step is to ensure that the compliance with food safety standards, such as MRLs, guarantees a negligible risk for the health of the consumer susceptible to ingest drug residues present in animal-derived food.

42. MRL values are established according to an approach which integrates both scientific data originating from risk assessment and criteria related to risk management. It is thus essential that JECFA scientific experts get involved in the setting of MRL values from data supplied by metabolism and tissue depletion kinetics studies while taking account of criteria pertaining to risk management and discribed in a risk assessment policy. CCRVDF, which is more particularly concerned with risk management, should carefully examine the MRLs suggested by JECFA to make sure, among others, that these management criteria are properly implemented.

43. If the available information does not make it possible to establish definitive MRLs, temporary MRLs can be proposed. The supplementary information necessary to establish definitive MRLs should be supplied within the time limit suggested by JECFA. If the supplementary information is not available at the expiry date or does not make it possible to establish definitive MRLs, the temporary MRLs are withdrawn. CCRVDF should come to a decision regarding these requests for supplementary information, the time delays suggested and the possible revocation or withdrawal of the temporary MRLs suggested.

2.4.1. Scientific criteria

44. MRL establishment must be based on the results supplied by metabolism and tissue depletion kinetics studies. These scientific studies should be performed in agreement with the guidelines established by JECFA in this area.

Information requested from JECFA

45. The JECFA is requested to indicate to CCRVDF

- the data necessary for the establishment of MRLs
- the protocols to be followed for metabolism and tissue residue depletion kinetics studies to supply JECFA with the required information

46. Protocols pertaining to tissue residue depletion kinetics should focus on the necessity of validating the analytical methods used to measure residue levels. The technical data supplied should make it possible to check that the methods used meet the requirements of intra-laboratory validation.

2.4.1.1. Marker residues

47. As modern analytical methods of residues in food are increasingly effective, in particular with regard to the specificity for the substances to be analysed, it is necessary to identify a residue, called marker residue, for each substance for which a MRL is established.

48. The justification of the marker residue is essential as far as

- the MRL is expressed in relation to this residue
- it is the basis of analytical controls

49. The principle of such justification relies on the possibility of estimating the level of total residues for a given tissue at a given time from the level of the marker residue. It is thus essential that the data originating from residue metabolism and kinetics studies, which have to be performed with radiolabelled drug, make it possible to establish a constant and known ratio between the levels of this marker residue and those of the

total residues for edible tissues over a period long enough which has to be relevant with regard to the probable withdrawal periods.

Information requested from JECFA

50. The JECFA is requested to indicate to CCRVDF

- whether the necessary relevant information is supplied to it, so that it can justify the choice of the marker residue for each tissue/food originating from each of the animal species concerned.
- if no, according to the experience acquired , whether it would be possible to define a marker residue for other foods and animal species for which no information is available by extrapolating from data supplied for certain foods and animal species and, if yes, in what conditions.
- whether the approach followed in this area by JMPR is equivalent to the approach currently used by JECFA and, if not, to compare the advantages and drawbacks of these two systems.

2.4.1.2. MRL values

51. The MRL values established for a given substance for the various foods/tissues originating from a treated animal must be defined from residue levels measured in these foods/tissues at a given time after the treatment. If the residue levels in the various edible tissues are different, these differences should lead to different MRL values for these different tissues.

52. Moreover, although JECFA does not have to determine withdrawal periods which depend on the various specifications characterising each veterinary medicinal product, it is essential that MRL values be nevertheless established on the basis of a practicable withdrawal time, justified by statistical studies and which ensures the public health protection.

Information requested from JECFA

53. The JECFA is requested to indicate to CCRVDF:

- the relationships between the statistical bases chosen to define MRL values ensuring consumer health protection and those used to establish withdrawal times, which have the same objective, in order to avoid a possible redundancy in the use of these statistics.
- the advantages and drawbacks of expressing MRLs in µg/kg or in mg/kg by taking into account in particular the impact of the units chosen to express MRLs on certain specifications of analytical methods (precision, accuracy)
- the advantages and drawbacks of expressing MRL established for lipophilic substances in relation to the fat content of animal-derived food, as done by JMPR

2.4.2. Management criteria

2.4.2.1. Marker residue

54. As far as an MRL represents a standard which can be used effectively to control residues of veterinary drugs in foods by official laboratories equipped for the control of drug residues in foods, it is essential that:

- marker residues are available on the market
- the methods chosen for the analysis of marker residues can be easily implemented.

Information requested from JECFA

55. The JECFA is requested to advise the CCRVDF wether it is appropriate to recommend, as often as possible, the parent substance be chosen as marker residue

2.4.2.2. Percentage of the ADI used

56. The ADI represents the maximum quantity of residues that a consumer can ingest daily during lifetime without appreciable risk to his health. Nevertheless, even though it is possible, or desirable, to establish lower MRLs which lead to a theoretical residue intake lower than the ADI established, this option should be chosen as far as it improves the safety of food and public health protection. Among the reasons which justify the use of this option, the following can be mentioned:

- the consideration of good practices for the use of veterinary medicinal products, which can involve complying with the withdrawal period leading to MRLs lower than those which were calculated from the corresponding ADI.
- the harmonisation of the MRLs established between the various animal species to which the substance can be administered in veterinary medicine.

57. This approach has already been followed by JECFA because, for example, the MRLs established for azaperone lead to a dietary theoretical daily intake of its residues which represents only 10% of the corresponding ADI, while the MRLs established for imidocarb lead to a dietary intake equivalent to almost the whole ADI.

58. However, the implementation of this option should be reasoned to avoid that

- it unfairly penalises certain substances assessed compared to others
- it hinders the use of substances in veterinary medicine in compliance with the good practices currently in force
- it leads to the establishment of MRLs which cannot be controlled with practicable analytical methods which could have been used if this option had not been implemented.

Information requested from JECFA

59. The JECFA is requested to indicate to CCRVDF in the assessment report, when it is the case, to justify the proposal of MRL values lower than those which could have been consider in order to comply with the established ADI.

2.4.2.3. Allocation of the ADI between foods

60. When a drug substance is intended to be administered to animals producing meat, milk and eggs, the allocation of the theoretical daily residue intake allowed between these various foods, based on the ADI established, is done pragmatically in order to improve the conditions of use of this substance in veterinary medicine.

Information requested from the JECFA

61. JECFA is requested to make clear, in the reports transmitted to the CCRVDF, the choices made for allocating the ADI between the different animal derived food so that they can be discussed by this committee. If necessary, several options can be suggested by JECFA.

2.4.2.4. Harmonisation of MRL values between various animal species

62. While it is necessary that the MRL values are established for the various tissues (muscle, fat, liver, kidney) in proportions that reflect the distribution of residues between these tissues, it is also important not to forget the problems raised by the establishment of MRLs for a drug substance intended to be administered to various animal species since they can vary from one species to another.

63. As far as the establishment of MRLs aims at guaranteeing the safety of foods, it is essential not to make the public believe that the safety of foods from various animal species is not equivalent because the values of the MRLs established for the same substance and the same food differ from on animal species to another.

64. Moreover, the establishment of different MRL values for the same tissue among the animal species concerned makes it significantly more difficult to establish, validate and implement analytical methods used in the surveillance of veterinary drug residues in foods.

65. The fact that MRL values established for a given substance can differ from an animal species to another for the same food makes it necessary to perform residue metabolism and tissue depletion studies in all the animal species susceptible to be treated by this substance. As the cost of these studies leads the veterinary pharmaceutical industry to limit these studies only to the animal species representing a major economic market, it appears that

- MRLs are not established for all the animal species to which a substance is intended, mainly for the so-called minor animal species
- the Codex procedure loses its efficiency with regard to the
  - consumer health protection against foods for which no international food standards guarantee their safety as far as residues are concerned
  - facilitation of the international trade of animal-derived foods for which the absence of MRLs represents a potential source of conflicts
- the national authorities in charge of the registration of veterinary medicinal products, which rely on the MRLs established by Codex when they do not have their own system for establishing MRLs, have to limit the animal species concerned by these marketing authorisations to those for which MRLs were established. This leads to an increase in the off-label use of veterinary medicinal products, which is not an improvement in the prudent use of veterinary medicinal products and public health protection.

Information requested from JECFA

66. As far as, after the 54th session of JECFA,

- The expert committee has established identical MRLs for 31 of the 41 substances intended to various animal species
- these 31 substances correspond to various therapeutical groups usually used in veterinary medicine.

the JECFA is requested to consider the different MRLs established for the other 10 substances and the significance of these differences in terms of consumer health protection in order to indicate CCRVDF, on the basis of a risk analysis for public health and the experience acquired in 12 years of work, whether it is really necessary to maintain these differences between these MRLs.

67. To do this, CCRVDF recommends that JECFA takes account of

- the similarity of the metabolisms of these 10 substances, which led to always choose the same marker residue
- the establishment, for some of these 10 substances, of identical MRL for a tissue and not for others or for certain animal species and not for others
- the necessarily relative accuracy of the residue levels due to the limited number and the variability of the available data
- the flexibility offered by the adjustment of the percentage of usable ADI and the duration of withdrawal periods.
- the limited significance of these differences between MRLs in terms of consumer health protection compared to the impact of various assumptions and safety factors used to this end during the hazard identification, hazard characterisation and exposure assessment steps of the risk assessment procedure.
- In addition JECFA is requested to propose and substantiate a definition of major and minor animal species

2.4.2.5. Foods concerned by MRLs

68. MRLs have to be established for all foods originating from animals to which a drug substance assessed by JECFA is intended.

Recommendations for JECFA

69. If residue levels in various tissues (muscle, fat, liver and kidney) can be very different, JECFA is requested to recommend in its assessment reports which tissues should be chosen as target tissue to be sampled as part of residue surveillance plans.

70. It is important to establish MRLs for muscle or fat to allow the control of the safety of carcasses moving in international trade.

71. When the residue levels in a tissue at the end of an appropriate withdrawal time are too low to establish both an MRL and a practicable control by available analytical methods, JECFA is recommended to indicate in the assessment report of this substance that it is not possible to establish an MRL for this tissue based on the usual methodology and to specify the reasons.

72. Nevertheless, in order to help member states which could occasionally wish to control the residues of a given substance in this edible tissue, JECFA is recommended to indicate in its assessment report an indicative value deduced from the quantification limit of the analytical method which can be used, while insisting on the fact that this tissue does not represent an adequate sampling basis for a surveillance plan for residues in foods.

73. Another difficulty arises when the calculation of MRLs to be in compliance with the ADI leads to the establishment of a withdrawal period that is too long for good production practices. In this case, JECFA is requested to specify this difficulty to CCRVDF by clearly describing the situation it in its assessment report.

2.4.2.6. MRL control

74. The desire to guarantee the safety of animal-derived food led member states to implement drug residues surveillance plans intended to check the compliance with established MRLs.

75. To increase the efficacy of these controls and to reduce their cost, the recourse to so-called multi-residue methods, enhanced by the use of more effective detectors such as mass detectors, widespreads regularly. For consistency in the determination of compliance with MRLs, it would be important that uniform criteria for the performance of such multiresidue method be developped and acceptable to all parties.

76. In this context, the analytical methods used in residue tissue depletion studies, which have to be validated, represent a major technical support for member states which can integrate them in a way or another in their control strategies according to the equipment they have and the sampling they have determined as a function of national animal production.

ANNEX 2

RISK MANAGEMENT AND CODEX PROCEDURE FOR ESTABLISHING MRLS OF VETERINARY MEDICINAL PRODUCTS

RECOMMENDATIONS TO CCRVDF

INTRODUCTION

1. As its work is followed by member state delegations mainly made up of authorities in charge of the management of veterinary medicinal products, CCRVDF has consequently authority to take account of criteria pertaining to risk management in participating in the setting of MRLs for veterinary medicinal products. Its involvement should preferentially concern the risk evaluation and management option assessment steps as the implementation of management options and the follow-up of this implementation are mostly the responsibility of member states only.

1. RISK EVALUATION

2. In this step of risk management, two components deserve particular attention in relation to the missions of CCRVDF : the ranking of the hazards, for determining the risk assessment and risk management priorities, and the consideration of the result of risk assessment.

1.1. Ranking of hazards

1.1.1. Inclusion criteria on priority lists

3. CCRVDF has to establish priority lists of drug substances for which MRLs need to be established and which have to be subjected to JECFA assessment. At its first meeting in 1986, CCRVDF adopted the criteria to be taken into account to do this. Lately, at its eighth meeting held in 1994, CCRVDF found it useful to modify the wording of these criteria but the Codex Commission does not seem to have validated this proposal of modification.

Recommendation no.1

4. It is recommended that CCRVDF clears up the uncertainty of whether the substance to be assessed must be marketed or not. The 1986 statement unambiguously indicates that the veterinary medicinal product must be marketed as far as it indicates that the product is present as residues in food products and that it largely affects world trade. The 1994 criteria are less precise because it only indicates that the drug is available as a commercial product and that it is susceptible to cause commercial difficulties, so that the inclusion of a non marketed substance liable to cause problems on a priority list is possible.

1.1.2. Presentation of candidate substances

5. As far as one of the selection criteria for candidate substances is that the information necessary for JECFA assessment be available, de facto only the veterinary pharmaceutical industry currently proposes substances for inclusion in the priority lists through the respective Member country of Codex because it is the only one to have dossiers containing the requested technical information.

Recommendation no.2

6. It is recommended that CCRVDF consider to include in the priority list candidate substances proposed by the members countries of Codex, on the basis of the technical dossier provided by the veterinary pharmaceutical industry during a procedure of MRL establishment or of marketing authorisation. This initiative, placed under the responsibility of the members countries of Codex, should be taken in liaison with the veterinary pharmaceutical company responsible of the concerned substance. This alternative option would present the advantage of better equilibrate the content of priority lists which would associate substances of importance for commercial strategies of the veterinary pharmaceutical industry and priority

substances with respect to the public health concerns of member states.

1.2. Consideration of the results of risk assessment

7. As far as

- Risk assessment must be performed in agreement with the risk assessment policy established by CCRVDF with the help of JECFA experts
- The establishment of MRLs by JECFA involves using a number of criteria pertaining to risk management
- CCRVDF can take account of other risk management criteria than those described in the risk assessment policy for the assessment of ADI and MRL proposals made by JECFA.

it is essential that CCRVDF puts more efforts in the critical assessment of JECFA proposals.

Recommendation no.3

8. It is recommended that Member countries of Codex receive from the JECFA secretariat the assessment reports relating to the concerned substances, even as draft reports, before the CCRVDF meeting. A minimum period of two months1 before the CCRVDF meeting should be enough to allow a close examination.

2. MANAGEMENT OPTION ASSESSMENT

9. The final objective of this component of risk management is to choose the appropriate management option, i.e. in this case to accept or not JECFA proposals for MRLs

10. In addition to the critical assessment of JECFA proposals made during the previous step, CCRVDF could also consider management criteria, which are currently discussed within the Codex Committee on General Principles, differing from those indicated in the risk assessment policy and which have already been taken into account by JECFA.

11. This particularly includes the global acceptance of food standards in general and MRLs in particular by member states anxious to avoid the rejection of a food, an animal production by the public increasingly concerned by

- the organoleptic and nutritional quality of foods
- animal health and welfare protection
- respect for the environment

Recommendation no.4

12. It is recommended that CCRVDF, in the light of the work carried out within the Codex Committee on General Principles, gives further thought on these risk management criteria as well as on a transparent assessment of the benefit/risk ratio for various types of substances used in animal husbandry in order to facilitate the consensual adoption of the ADI and MRLs suggested by JECFA.

1 In agreement with Rule V.7 (availability of documents) of the Rules of Procedure of the Codex Alimentarius Commission.