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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DISCUSSION PAPER ON DATA REQUIREMENTS FOR THE ESTABLISHMENT OF MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS FOR MINOR SPECIES

(Prepared by FAO Joint Secretary to JECFA)

BACKGROUND

1. The Committee at its 11th Session in 1998 was informed that the issue of data requirements for minor species was discussed at the 48th JECFA meeting. The Committee accepted the offer of the Delegation of New Zealand to prepare a discussion paper on data requirements for the establishment of Maximum Residue Limits for Veterinary Drugs for Minor Species for consideration at the 12th Session. The FAO Secretary to JECFA also agreed to present a document concerning the 52nd JECFA discussions on this subject for consideration by the 12th Session of the Committee. (ALINORM 99/31, paras 129-130)

GUIDELINES ON THE ESTABLISHMENT OF MRLS IN MINOR SPECIES

PROBLEM STATEMENT:

2. Since the beginning of the work carried out by the JECFA, very few MRLs have been allocated for therapeutic substances intended for the so called minor animal species. This problem has already been identified since long and both competent authorities and veterinary pharmaceutical industry have expressed their concerns in this respect.

3. This absence of MRLs for minor animal species raises real problems for an appropriate protection of human health with regard to veterinary drug residues likely to be found in the food commodities derived from these animals. The lack of MRLs prevents the competent authorities to

- establish appropriate withdrawal times, which are the only operational concept to provide the guarantee to the consumer that veterinary drugs are properly used with regard to veterinary drug residues in food,
- organise the control of veterinary drug residues in food commodities derived from these animals within the framework of national residue monitoring and surveillance programmes.

4. Consequently, there is an urgent need to agree upon a practical and enforceable procedure to adequately protect public health in respect to veterinary drug residues. A new approach, based on the concept of risk analysis which both associates risk assessment and risk management, should be considered.

5. As a first step, this contribution is limited to propose an approach for establishing MRLs in minor animal species for substances already allocated MRLs for major animal species.

6. The more complicated case of establishing MRLs for substances only intended for minor animal species will be considered in a second step at a later stage.

1. DEFINITION OF MINOR ANIMAL SPECIES

7. Minor animal species could be defined as being those which are not included in the following list of major animal species :

- . Cattle and Sheep (meat)
- . Cattle (milk)
- . Pigs
- . Chickens (including eggs)

8. A special consideration to Salmonidae will be given later on in paragraph 3.

2. POSSIBLE EXTRAPOLATION FROM MAJOR TO MINOR ANIMAL SPECIES

9. Subject to the procedure to be used in order to implement this concept, an extrapolation should be based on the following correspondences between major and minor animal species as indicated in the table.

Major species and their products	Extrapolate to	Minor Species
Cattle and sheep meat		other ruminant meat
Cattle milk		other ruminant milk
Poultry and eggs		other avian species and eggs, including turkeys
Relevant species (e.g. ruminants, pigs)		horse / rabbit

2.1 Cases in which no MRLs are needed for a substance intended for a corresponding minor animal species

10. The following situations could be considered as cases in which it would not be necessary to establish MRLs for the intended use of a substance in a corresponding minor animal species:

- occasional use of the substance,
- intended treatment of a limited number of animals,
- administration to animals long enough before slaughter (one month).

11. The applicability of these criteria has to be demonstrated by appropriate information provided by the sponsor to JECFA. Following an evaluation of this information JECFA will forward its recommendation to CCRVDF.

2.2 Cases in which MRLs have to be established for a substance intended for a corresponding minor animal species

12. The question is to ascertain to what extent and in what conditions a MRL (final or provisional) established for a major animal species can be extrapolated to the corresponding minor animal species.

In order to answer this question, the following four issues must be addressed.

2.2.1. The numerical values of MRLS

13. Taking into consideration the concept of the substitution of the food commodities, which means that when a consumer eats 300 g of meat of one animal species, he does not eat, the same day, 300 g of meat of another animal species, the MRL value should be the same. In case of some differences in the residue depletion studies and residue distribution in tissues between the major and minor animal species which could impact the length of the withdrawal time, the competent authorities will adopt appropriate decisions for the minor animal species during the marketing approval procedure.

2.2.2. Identification of the marker residue

14. This is the main issue to be considered for an appropriate extrapolation from the major animal species to the minor one.

15. It should be kept in mind that up to now for all the substances evaluated under the European MRL procedures and for which MRLs have been assigned either on a permanent or provisional basis the same marker residue applies to all tissues of all different major animal species concerned. It therefore can be considered that there is evidence to assume that the same residue will be the marker residue in all animal species and it could be possible to accept this extrapolation according which the marker residue accepted for one major animal species could also be valid for the corresponding minor animal species.

16. However, two questions are to be addressed and to be confirmed by the appropriate information:

1. Does the marker residue, established for the corresponding major animal species, also exist in the minor animal species under consideration and can it be used in practice for the purpose of monitoring programmes of residues.

   In order to address this first question the sponsor should carry out an appropriate residue depletion study in the minor animal species under consideration. By doing so, the sponsor should prove with a properly validated method (see point 4.4 validation of analytical methods) that the marker residue, established in the corresponding major animal species

   - does exist in the corresponding target tissues (see point 4.3 target tissues)
   - is present in those target tissues in concentrations high enough for this marker residue to be used for the control of veterinary drug residues in food?

   In the case these two requirements are not met, the sponsor would have to carry out additional studies in order to identify an appropriate marker residue.

2. Is the ratio between this marker residue and the total residues which are usually related to by the ADI likely to be similar in major and minor animal species?

   This second question should be considered by referring to the risk analysis concept.

   Considering

   - the different safety factors used in the establishment of the ADI and of the amount of the daily ingested food,
   - the conservative procedure used to establish withdrawal times,
   - the limited consumption of food commodities derived from minor animal species,

   it can be concluded that the possibly remaining uncertainty about the ratio of the marker to the total residue in the corresponding minor animal species is unlikely to raise any concern to public health.

2.3 Target tissues

17. The target tissues of the corresponding major and minor animal species should be the same. When, in application of the general rule of JECFA, numerical values have to be assigned to the four tissues muscle, fat, liver and kidney, indication should be given to the competent authorities in charge of residue control in food about the relevant target tissues to be used for the purpose of monitoring. Residue monitoring could be limited to one or two tissues according to the minor animal species under consideration.

2.4 Validation of analytical method

18. An analytical method properly validated for the control of MRLs in a major animal species can principally be considered as applicable for the control of MRLs in minor species if the following tests are carried out :

- determination of the limit of detection of the method.

- determination of the limit of quantification at residue concentrations corresponding to half of the MRL or the MRL values. This determination could be carried out at each concentration, with five replicates, during three consecutive days. Therefore the statistical analysis will provide the needed information in respect of the accuracy, repeatability and reproducibility.

3. SALMONIDAE

19. It has to be recognized that only a very limited number of MRLs have been allocated to the therapeutic substances commonly used in fish farming.

20. Due to the increasing consumption of salmonidae, these animals could be classified among the major animal species.

21. There is increasing concern about the availability of authorised substances for the treatment of salmonidae on one side and the lack of regulatory instruments to control residues in these species on the other side.

22. Therefore it could be appropriate to consider some relaxation regarding the technical data to be required for the establishment of MRLs in salmonidae.

23. The following considerations could support this proposal:

- So far, for substances investigated, the marker residues determined for salmonidae have been identical to those identified in the other animal species.
- for salmonidae, the only food commodity to be considered is muscle (plus skin). In all animal species, including salmonidae, muscle is not a tissue in which a very significant metabolism takes place. Therefore the parent compound could be very often accepted as a valid marker.
- even if, so far, the studies comparing the metabolism of veterinary drugs in salmonidae and other animal species are rather scarce, the available data do not highlight significant differences between these animal species. It seems that the only difference lies in the speed at which the substances are metabolised. It appears that, in fish, the metabolism could be slower, specifically when the temperature of the water fishes are living in is rather cold. Therefore, these remarks provide an additional support for the parent compound to be considered as appropriate marker residue.

24. In conclusion it could be considered that the rationale proposed in this text for establishing MRLs for minor animal species could also apply to salmonidae. As it has already been said, muscle being the only food item to be considered for salmonidae, the implementation of the proposed extrapolation implies that a MRL be always established for muscle in major animal species.

25. In consequence, the data requirements for minor species as laid down in paragraph 2.2. do also apply for salmonidae.

4. BEES

26. Honey is definitively a marginal food item and all the comments already made about the limited number of MRLs established for minor animal species apply particularly to honey. Therefore a pragmatic approach should be agreed upon in order to establish MRLs for the limited number of the therapeutic substances used in this area.

27. This pragmatic approach is also justified by the fact that, if the good husbandry practices are observed, the likelihood to find residues in honey is very limited. So, it is not recommended to treat bees when they are collecting the flower nectar and storing it in the hives. For technical reason, this treatment, which would result in contamination of honey by residues, is not effective and, usually, these treatments are carried out at least two weeks before the bees start to collect nectar. Therefore, they have already eliminated the main part of the drugs they have absorbed.

28. In addition there are two dilution factors which result in decreasing the concentration of residues in honey. First, for the case, even treated at least two weeks before collecting the nectar, bees contaminate the very first amounts of produced honey, the rest of the production will result in diluting this possible early contamination. The second dilution factor comes from the fact that the farmer usually

treats the bees at the beginning of the outbreak. He does not wait that all the hives are attacked by the disease. Usually only 10% to 20 % of the hives are treated.

29. Therefore the following practical approach is suggested for establishing MRLs for honey:

- The parent compound is considered as the marker if the sponsor is able to prove with a properly validated method that the parent compound can be found in honey after the substance under consideration has been given to bees.
- The numerical value of the MRLs is determined from a residue depletion study at different harvest time points in order to
  - . estimate the daily ingested residues in comparison to the established ADI.
  - . be consistent with the LOQ of the proposed analytical method.

30. In the special case of bees and when establishing MRLs for honey, consideration has to be given to the final formulation of the product and the mode of application, as those factors may significantly impact the occurrence of residues in honey.