CODEX ALIMENTARIUS COMMISSION E

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twenty-fourth Session

DISCUSSION PAPER ON MRLS FOR GROUPS OF FISH SPECIES

Report of the CCRVDF Electronic Working Group on Extrapolation of MRLs for Veterinary Drugs to Additional Species and Tissues, prepared by Norway and Japan with the assistance of Argentina, Belgium, Brazil, Chile, Canada, France, Japan, Peru, Thailand and United States.

BACKGROUND

Mandate

1. CCRVDF23 (Houston, Texas, 2016)agreed to establish an EWG with the aim to develop a discussion paper on the feasibility of establishing MRLs for groups of fish species for veterinary drugs being considered by JECFA/CCRVDF in the light of:

   i) Public health

   ii) International trade

2. The paper shall consider what grouping might be appropriate for finfish, crustaceans and molluscs (para 17-18 of the REP17/RVDF).

3. The EWG was to be led by Norway and co-hosted by Japan and working in English only. Translation was to be performed by Chile (Spanish) and Senegal (French).

Grouping of fish

4. The 78th and 81st JECFA has concluded that information on adequate groupings of fish is necessary to evaluate if it is feasible to extrapolate MRLs to other similar species.

5. Several principles for groupings of fish species may be applied based on e.g.:

   - common aquaculture environment (salinity and temperature)
   - phylogeny or common physiology (high lipid or low lipid)
   - common behaviour (demersal or not, type of diets)

ISSUES

6. The absence of MRLs for veterinary drugs[1] in fish species raises challenges for appropriate protection of human health and fair trade practices. So far, there are only five compounds with established MRLs.

7. Lack of MRLs for fish species reduces the variety of drugs available to treat diseases, and thus affects the possibility of maintaining good fish health by veterinary treatments in aquaculture. Extrapolating to several fish would contribute to expand the variety of available drugs for fish. Extrapolating MRLs will also reduce the number of studies performed with animals and thus follow the principles of replacement, refinement and reduction principles for animal welfare.

[1] 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 behaviour. (Codex Procedural Manual 25th edition)

8. For fish[2] there are a wide range of species farmed as food-producing animals, compared to farmed mammals or birds. Residue studies on all species for any drug is costly and therefore extrapolating[3] MRLs is considered necessary.

9. The challenges of extrapolating MRLs to other fish species have been raised by JECFA at several sessions of CCRVDF based on the understanding that there might be a need for grouping.

INTRODUCTION

10. The EWG has discussed possibilities for extrapolating MRLs evaluated for single species to one group or more as simple as possible, and at the same time maintaining the food safety. The work of this EWG has been concentrating on:

i. The need to extrapolate

ii. Limitations for extrapolation

iii. Extrapolation principles

i. The need to extrapolate

11. The main reasons for extrapolating are to reduce resources necessary for MRL evaluation, protecting the health of consumers, ensuring fair practices in food trade and increase fish health and fish welfare.

12. So far, only five veterinary drugs are given MRLs by Codex[4]. In most of these evaluations, the residue information reviewed by JECFA was primarily from the peer-reviewed scientific literature and reports from government laboratories and agencies.

13. Of the five substances for which JECFA has made recommendations of MRLs for finfish, two have been for “fish” and three for “salmon” and/or “trout”, based on the information provided. For the substances for which recommendations have been for “fish”, data have been provided for three or more diverse species of finfish.

14. Three substances have been evaluated by JECFA for use in the production of crustaceans; in all three cases, residue data provided were only for giant prawn, also known as Black tiger shrimp (*Paeneus monodon*).

***Table 1**. Veterinary drugs for fish and crustaceans evaluated by JECFA*

Veterinary drug	Group of species	Additional species	Conclusion	Additional
Chloramphenicol	-	-	No ADI/MRL	
Gentian violet	-	-	No ADI/MRL	
Malachite green	-	-	No ADI/MRL	
Deltamethrin	Salmon		MRL 30 µg/kg	
Diflubenzuron	Fish	Salmon and cod	No ADI/MRL	
Emamectin benzoate	Salmon	Trout	MRL 100 µg/kg	
Flumequine	Black tiger shrimp*/Trout		MRL 500 µg/kg	
Oxolinic acid	-	-	No ADI/MRL	
Oxytetracycline	Muscle (fish) & tiger prawn	-	MRL 200 µg/kg	
Teflubenzuron	Salmonids		MRL 400 µg/kg	
Amoxicillin	Catfish		Withdrawn	Insufficient data
Thiamphenicol	Fish		Withdrawn temporary MRL	Insufficient data submitted

*MRL for Black tiger shrimp was not adopted by CCRVDF.

15. JECFA has not been requested by CCRVDF to recommend MRLs for any veterinary drug in any species of molluscs to date nor received any data regarding such use. Any comment on the feasibility of extrapolation of MRLs for mollusc species would therefore be speculative.

[2] Fish: Any of the cold - blooded (ectothermic) aquatic vertebrates. Amphibians and aquatic reptiles are not included (CAC/RCP 52-2003)

[3] Extrapolating MRLs means the process of fusing existing MRLs to estimate residue levels to other species for which no conventional residue data is available. WHO: Principles and Methods for the Risk Assessment of Chemicals in Food.

[4] Adopted by CAC.

16. EWG members submitted information on more than 50 different registered medicines for fish or crustaceans, and as shown above, only five of these are given MRLs by Codex. The major target fish orders submitted where Perciformes (30 compounds), Salmoniformes (28 compounds) and Decapoda (19 compounds). This shows a need for extrapolation for compounds not yet evaluated by JECFA. An evaluation from JECFA of the remaining more than 45 compounds in all aquaculture species, will take up JECFAs limited resources. CCRVDF should therefore seek to find a cost-effective way forward.

iii. Extrapolation principles

17. JECFA has given guidance on the criteria/assumptions currently used for interspecies extrapolations, including minimum data required to support such extrapolations among physiologically related species and extrapolation to additional minor species.

18. The report of the 78th JECFA recommended terms for fish and other seafood[5]:

- The term «fish» should be used when a MRL-recommendation applies to multiple species of fin fish;
- The term “mollusc” should be used for species such as clams, oysters and scallop; and
- The term “crustaceans” should be used for species such as shrimp, prawn and cray fish.

19. The following principles have been given by JECFA before evaluating:

- The drug must have existing approval for use in the species for which MRL extrapolation is requested in at least one CODEX member state;
- The drug must have a label or a statement of the approved conditions of use ((GVP[6]); and
- When recommendations of a MRL are for a specific species of fish or seafood, this will be reflected in the risk assessment.

20. EHC 240 states that for substances with MRLs recommended in one or more species, MRLs could be extended to a related species provided that the metabolic profile is comparable, the marker residue is present in the species for which the extensions is considered at sufficient levels for monitoring by validated analytical methods and there is an approved use.[7] Fish is included in the EHC, but not discussed in regards to extrapolation, however the information might still be useful in this discussion.

DISCUSSION

ADI and MRL

21. JECFA evaluates veterinary drugs to establish safe levels of intake and develop draft MRLs when veterinary drugs are used in accordance with good veterinary practice. MRLs of veterinary drugs in fish are proposed at levels that can be reached within practical withdrawal times. JECFA also estimates potential intake of residues of veterinary drugs and standard assumptions about the consumption of animal products. These estimates of potential intakes are compared with the ADIs.

22. Safety assessment of a drug (toxicity studies and ADI) has been done independent of the target animal species. The ADI is assigned to a drug, but the residue levels of that drug will vary widely between species. The consumption factor in a diet of a species has a major impact on setting MRLs. However, a poorly researched species would rarely be consumed to a greater scale than traditional species. JECFA estimates dietary exposure for veterinary drugs from fish based on consumption data of overall fish, not each fish species data. The estimated dietary exposure might not be changed if the MRL for one fish species extrapolates to another fish species. One of the most important considerations in determining MRLs in products from animal origin is the amount of food used for these calculations.

[5] WHO Technical Report Series, Evaluation of certain veterinary drug residues in food, no 988

[6] Good Practice in the Use of Veterinary Drugs (GPVD) is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions (definitions adopted by the Codex Alimentarius Commission – Codex Procedural Manual).

[7] http://apps.who.int/iris/bitstream/10665/44065/11/WHO_EHC_240_11_eng_Chapter8.pdf?ua=1

Evaluating veterinary drugs by JECFA.

23. To assess the risk for consumption of residues of veterinary drugs, the 32nd JECFA[8] identified the need for the following information to be evaluated.

- use patterns – good veterinary or husbandry practices including purpose of use, doses, methods of administration;
- pharmacological characteristics;
- analytical criteria;
- metabolism and pharmacokinetics;
- toxicology data; and
- residue depletion studies under field conditions.

24. If JECFA is going to extrapolate MRLs to groups of fish without sufficient data on withdrawal times, the MRLs will be conservative. Still, there is a possibility of accepting conservative data meanwhile JECFA evaluates MRLs for species with sufficient data. This approach will probably mean different MRLs for the groups of fish.

The VICH-guideline

25. The VICH-regions have prepared four guidelines (VICH-GL46-49)[9] to facilitate the mutual acceptance of metabolism and residue depletion data for veterinary drugs used in food-producing animals by national/regional regulators. The objective of the guidelines are to provide study design recommendations which will facilitate the universal acceptance of the generated metabolism and residue depletion data to fulfil the national/regional requirements.

26. The scope of the guidelines are amongst others to give suitable methods to generate data suitable for elaboration of appropriate withdrawal times to address consumer safety concerns. VICH has developed a draft guideline (draft VICH-GL 57)[10] for residue depletion study in aquatic species. In regards of finding appropriate withdrawal times, it is of most importance to group (e.g. same order) the study conditions of several parameters, such as salinity and water temperature. The draft VICH-GL57 also recommends using representative species for each group.

Withdrawal times and Good Veterinary Practice

27. In the procedural manual[11] Good practice in the Use of Veterinary Drugs is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions.

28. The 34th JECFA[12] noted that the determination of the appropriate withdrawal time for a given veterinary drug such that its use complies with the MRL is the responsibility of national licensing authorities. JECFA, when deriving MRLs, verifies that the MRLs it recommends can be achieved through practical withdrawal times and application of good practices in the use of veterinary drug. There have been instances in JECFA evaluations where it has recommended against use of a veterinary drug (e.g. levamisole in eggs for laying birds and milk for lactating cows) because residues were very high at practical withdrawal time and the time necessary for depletion of residues could not be achieved in normal agricultural practice.

29. A withdrawal time, as recommended by the 38th JECFA, should be established on the basis of a statistical limit. JECFA agreed to use the 99th percentile with a 95% confidence level for verifying that recommended MRLs can be achieved through realistic withdrawal times. This is because a withdrawal time based on a mean value of a set of residue data may result in instances where failure to comply with the MRL may occur in a considerable number of samples in a residue control program.

30. The EWG has discussed the possibility of extrapolating MRLs to all finfish based on the fact that safety assessment of a drug is based on the ADI and the fish intake is included in the protein ration of the consumption data independently of the species. It will however, depend on each country's risk assessment when the drug is evaluated for Marketing Authorization which withdrawal time is set for each species. The withdrawal time needs to be adjusted to water temperature, common physiology and phylogeny.

[8] http://www.who.int/foodsafety/chem/jecfa/decision_tree_mar_2009_final_for_web.pdf
[9] http://www.vichsec.org/guidelines/pharmaceuticals/pharma-safety/metabolism-and-residue-kinetics.html
[10] http://www.vichsec.org/consultations/active-draft-guidelines.html
[11] http://www.fao.org/3/a-i5995e.pdf
[12] http://www.fao.org/fileadmin/templates/agns/pdf/jecfa/2000-06-30_JECFA_Procedures_MRLVD.pdf

31. One of the objectives of this EWG is to find ways to be more flexible in extrapolating MRLS from one species to a widest spectrum of finfish species as possible without risking food safety. As so few drugs have been evaluated by JECFA, there is a need for finding ways to extrapolate.

Salinity and temperature

32. Temperature and salinity are important factors of absorption, metabolism and excretion of the drugs and will influence the residue depletion time. However, based on feedback from EWG members, temperature and salinity are not likely to influence on the metabolic pathway of the drug, and the marker residue will not be affected by salinity and temperature. The safety of the drug will therefore depend on the dosage and administration, withdrawal times and other conditions set in the approval of the drug. Representative species and recommended water temperature for the residue depletion studies for a single order claim are shown in the VICH draft GL 57 guidelines.

Phylogeny or common physiology

33. Most drugs are lipophilic. Lipid content may influence retention of lipophilic substances. The lipid content in the fish or the metabolic pathway varies. There is so far no harmonized fish groupings according to fat contents, however drug metabolizing enzymes (CYP450s) can be similar between closely related strains. If grouping according to fat levels, there is a need for grouping of fish according to fat content. There is a wide variety of lipid content even within the same order of fish, it is therefore difficult to set up harmonized fish groups and to specify their representative fish species based on phylogeny and common physiology.

Common behaviour

34. Metabolism might be different between carnivorous and herbivorous species and thus the time of elimination of the drug can vary. There is little evidence supporting grouping of fish according to their common behaviour, and it might therefore be difficult to set up harmonized rules for fish groups and to specify their representative fish species based on common behaviour.

Representative species

35. The 78th JECFA considered that it may be appropriate to identify some representative species of fish, such as salmon, and of seafood, such as shrimp (crustacean), as “major species” of fish and seafood.

36. Members of the EWG commented on ways to be flexible in extrapolating MRLs for one finfish species to other finfishes. Defining representative species may not either be the most efficient way of extrapolating MRLs nor increasing the food safety.

37. Being that the safety assessments of the drug has been done independent of the target animal species; the MRL can be transferred to any species without having to define “representative species”.

38. Minimum data are required for extrapolation and GVP (good veterinary practice) must be required.

CONCLUSION

39. Feedback from EWG members shows different views on the need for grouping. Some suggested grouping according to various combinations of salinity, temperature, phylogeny/common physiology and common behaviour, all in all four parameters.

40. When considering grouping, each of these four parameters must at least be divided into high and low. Altogether this will become 16 different groups of fish. Then taking into consideration that more than 45 drugs need to be evaluated for MRLs. Grouping of 45 drugs according to 16 different groups of fish means at least 720 evaluations, and up to 720 different MRLs. There is a need to consider the effectiveness of resources spent on grouping.

41. Until now, no grouping according to salinity, phylogeny/common physiology and common behaviour have been performed, so grouping according to these parameters needs to be performed before a final grouping can be done. The only approved grouping by fish order so far is performed by VICH. This grouping is for performing studies on withdrawal times on different temperature levels. However, there is still need for work to be done on grouping fish for extrapolating MRLs.

42. It was also suggested not grouping fish. This due to the fact that the ADI is set independently of the target animal species, and that safety assessments of the drug are done independently of the target animal species. Also, the MRLs recommended by JECFA secures that consumers are exposed to only a fraction of the acceptable daily intake (ADI) of the drug.

43. Food consumption data is the basis when MRLs are derived from ADI and food consumption data take into account the total amount of consumed fish regardless of fish species. Hence, MRL can be the same for all finfish species.

44. To ensure food safety, national risk management is crucial and can be based on GVP and sufficient withdrawal times. Sufficient withdrawal times will vary based on regional differences in temperature, salinity, phylogeny/common physiology, and common behaviour.

RECOMMENDATION

45. CCRVDF may wish to discuss the following options:

A. Grouping the fish according to temperature, salinity, phylogeny, common physiology and common behaviour as all the parameters are considered equally important by the members. This will sustain a considerable work for JECFA.

B. Extrapolating MRLs to all finfish with a conservative approach while waiting for sufficient data grouping according to temperature, salinity, phylogeny, common physiology and common behaviour. This may result in unnecessary conservative MRLs.

C. No grouping, but discuss further guidance on national risk management options as this might seem an effective way forward.

46. Other matters could have been considered further, based on comments made by EWG members:

- Grouping of drugs. Metabolism of drugs is driven by chemical nature. Small differences can cause different metabolism pathway. Based on the feedback from EWG members, it does not look like grouping of drugs neither should be essential nor necessary when extrapolating MRLs.
- Marker residue. Extrapolation is generally possible if the marker residue is identical and the same food basket is used for the species of one group, in this case the ADI cannot be exceeded.
- Antimicrobials. The use of antimicrobials in food animals can create an important source of antimicrobial resistant bacteria that can spread to humans through the food supply. Improved management of the use of antimicrobials in food animals, particularly reducing those critically important for human medicine, is an important step towards preserving the benefits of antimicrobials for people.

  When discussing extrapolating of antimicrobial drugs the work on minimizing antimicrobial resistance must also be taken into account as described in the *Code of practice to minimize and contain antimicrobial resistance*.[13]

REFERENCES

Codex Alimentarius - Glossary of terms

Code of practice to minimize and contain antimicrobial resistance CAC/RCP 61-2005

Commission Regulation (EU) 2017/880 of May 2017.

Critically important antimicrobials for human medicine

EMEA-Position paper regarding availability of veterinary medicinal products - extrapolation of MRLs

VICH draft guideline at step 4 of the VICH Process "Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-producing species: Marker Residue Depletion Studies to Establish Product Withdrawal Periods in Aquatic Species.

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WHO Technical Report Series, Evaluation of certain veterinary drug residues in food, no 988. Seventy-eighth report of the Joint FAO/WHO Expert Committee on Food Additives.)

WHO Technical Report Series, Evaluation of certain veterinary drug residues in food, no 997. Eighty-first report of the Joint FAO/WHO Expert Committee on Food Additives.

WHO list of critically important antimicrobials (WHO CIA list)

[13] *Code of practice to minimize and contain antimicrobial resistance* (CXC 61-2005)