codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 4 **CX/RVDF 01/4**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS
Thirteenth Session
Charleston, South Carolina, USA, 3-7 December 2001

CONSIDERATION OF DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS AT STEP 7

PART 1: COMMENTS SUBMITTED AT STEP 6 IN RESPONSE TO CL 2000/28-RVDF ON DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS LISTED IN ALINORM 01/31, APPENDIX V

BRAZIL

Clenbuterol

1. Brazil supports the advance to step 6, observing that in Brazil residue for this compound is not allowed.

Neomycin

2. Brazil supports the advance to step 6, observing that in Brazil only the formulation of oral use is registered.

Phoxim

3. Brazil supports that it be retained at step 5, waiting the result of the European Community's revision for subsequent positioning.

Porcine Somatotropin

4. Brazil supports the advance to step 6.

Thiamphenicol

5. Brazil supports the advance to step 6.

CANADA

6. Canada does not support the adoption of the proposed MRL for Clenbuterol as we believe there is insufficient data on the noted analytical method. Although JECFA (FAO Food and Nutrition Paper No. 41/9), provided a method which claimed a limit of quantitation (LOQ) of 0.05 µg/L (or 0.05 µg/kg using the revised MRL unit for milk), there was no data provided in support of that claim.

7. Canada believes that this MRL should be held until data supporting the claimed LOQ can be reviewed by JECFA or the CCRVDF Working Group on Methods of Analysis. The bottom line is that currently, there is no validated method to support the MRL for clenbuterol in milk.

FINLAND

Clenbuterol

8. The draft Codex MRL for milk can be supported.

Neomycin

9. Codex MRLs for bovine liver and kidney are remarkably higher that the EU MRLs. The analytical method available for liver and kidney is not fully validated. The proposed MRLs for liver and kidney cannot be supported.

Phoxim

10. The proposed MRLs can be supported except for milk.

Porcine Somatotropin

11. No comment.

Thiamphenicol

12. Due to inadequate information and lack of validated analytical method the Codex proposal cannot be supported.

HAITI

13. No comments.

SPAIN

Clenbuterol

14. We have no observations, as we are in agreement with the MRL for milk.

Neomycin

15. We propose the following MRLs:

Species	Tissue	MRL (µg/kg)
Cattle	Liver	500
Cattle	Kidney	5000

Phoxim

16. We propose the following MRLs:

Species	Tissue	MRL (µg/kg)
Porcine	Muscle	20
Porcine	Liver	20
Porcine	Kidney	20
Porcine	Fat	700

Thiamphenicol

17. We propose the following MRLs:

Species	Tissue	MRL (µg/kg)
Porcine	Liver	50
Porcine	Kidney	50

TURKEY

18. No comments.

UNITED STATES

Clenbuterol

19. The U.S. supports this MRL. The U.S. agrees with JECFA's determination that residues of clenbuterol in milk, resulting from use as a tocolytic agent in lactating dairy cattle, i.e., a single injection of 0.8 µg/kg bw, would not pose a risk to public health. Therefore, an MRL for milk could be recommended.

Neomycin

20. The US does not support the draft MRLs for Neomycin and recommends reevaluation by JECFA. New information has become available since the ADI was established (1996) by JECFA describing an inherited susceptibility to aminoglycoside ototoxicity resulting in rapid and irreversible hearing loss in genetically susceptible. As a result, we request that JECFA reevaluate the safety of neomycin particularly since neomycin ototoxicity primarily affects cochlear as opposed to vestibular function.

21. New information could support a request for JECFA to reevaluate the effects of neomycin on human intestinal microflora. From a study of neomycin in a chemostat system contracted by FDA, the preliminary results indicate a NOEL of 25 µg/kg/day for effects on human intestinal microflora. Effects seen at higher doses (250 and 2500 µg/kg/day) include an increase in resistant Enterococci.

Phoxim

22. The U.S. supports advancement of these TMRLs.

Porcine Somatotropin

23. The U.S. supports the decision of JECFA to classify MRLs for rpSTs as "not specified" and advance this to step 6. The U.S. is not aware of any scientific information that would question JECFA's conclusion that the use of porcine somatotropin poses no hazard to human health.

Thiamphenicol

24. U.S. supports the advancement of these TMRLs. Outstanding residue issues will be addressed at the 58th meeting of JECFA (February 2002).

EUROPEAN COMMUNITY

25. On request of the Commission services the competent committee for evaluation of maximum residue limits for pharmacologically active substances used in veterinary medicinal products, the Committee for Veterinary Medicinal Products, considered the Codex Circular letter 2000/28 -RVDF.

Clenbuterol

26. Clenbuterol (bovine milk): The European Community can accept the draft Codex MRLs as the value is in accordance with European Council Regulation (EEC) N° 2377/90.

Neomycin and Phoxim

27. It is recommended to accept the following draft Codex MRLs as these values do not differ significantly from those adopted by the European Community in accordance with Council Regulation (EEC) No 2377/90 and do not pose any risks with respect to consumer safety: neomycin and phoxim.

Porcine Somatotropin

28. For the following substance it is recommended that the European Community does not give the support for the proposed draft Codex MRLs: Porcine somatotropin. No safety and residue evaluation has been performed in the European Community, as no application was submitted.

Thiamphenicol

29. The European Community does not give support to the proposed draft Codex MRLs for thiamphenicol due to severe lack of reliable data for the determination of ADI and the ratio of marker to total residues. Very similar deficiencies were found in the dossier put forward by the JECFA and in that submitted to the European Community, on the basis of which it was not possible to establish definitive MRLs. [1]

Comparison EU (CVMP)/draft CCRVDF(JECFA)MRLs*:*

	ADI	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)			
				Muscle	Fat	Liver	Kidney
EU (CVMP)	2.5 µg/kg bw	Porcine	Thiamphenicol	-	-	-	-
		Fish	"	-			
Draft CCRVDF (JECFA)	0-5 µg/kg bw	Porcine	Sum of thiamphenicol and thiamphenicol conjugates, measured as thiamphenicol	50	50	100	500
		Fish	"	50*			

* *Muscle + skin*

30. The CVMP established a microbiological ADI of 2.5 µg/kg bw based on the mean MIC_{50} for *Fusobacterium* (0.50 µg/ml) and a bioavailable fraction of 0.5. This microbiological ADI, being lower than the toxicological one (45 µg/kg bw based on a NOEL of 9 mg/kg bw/day in a 13-week rat study and a safety factor of 200), was used for the calculation of MRLs.

31. The JECFA established a microbiological ADI of 4.58 µg/kg bw based on the mean MIC_{50} for *Fusobacterium* (0.50 µg/ml) and a bioavailable fraction of 0.4. In this case the JECFA considered that the NOEL of 5 mg/kg bw/day in the rat carcinogenicity study was the most relevant toxicological endpoint. Applying a safety factor of 100, the JECFA established a toxicological ADI of 0-50 µg/kg bw/day.

32. Although based on different endpoints, the toxicological ADIs set by the JECFA (0-50 µg/kg bw/day) and CVMP (45 µg/kg bw/day) are very similar.

[1] The European Community position is based on the following decision taken at the 24th session of the Codex Alimentarius : « When there is evidence that a risk to human health exists but scientific data are insufficient or incomplete, the Commisison should not proceed to elaborate a standard but should consider elaborating a related text, such as a code of practice, provided that such a text would be supported by the available scientific evidence » (ALINORM 01/41, para. 81)

33. The JECFA established temporary MRLs for fish and pig tissues. Due to lack of information on tissue metabolites, the marker residue was defined as the sum of thiamphenicol and thiamphenicol conjugates, measured as thiamphenicol. The JECFA noted that no data were available to determine the ratio of marker (MR) to total microbiologically active residues (TR) in any species. The JECFA recognized that thiamphenicol glucuronide is not microbiologically active, but could be converted in humans to microbiologically active parent drug after ingestion. Quantitative data on the presence of thiamphenicol glucuronide as a portion of the total residues were lacking. A validated analytical method for measuring the marker residue was not available. Furthermore, the JECFA felt that further work was needed to establish the distribution of metabolites in edible tissues.

34. In contrast to the JECFA, the CVMP identified the parent compound as marker residue. Similar to JECFA the CVMP considered the information on the ratio of marker residue to total microbiologically active residues inadequate and a lack of a validated analytical method.

35. In view of the deficiencies of the dossier assessed previously by the CVMP, the CVMP could not recommend the establishment of final MRLs for thiamphenicol for pigs and fin fish following the previous establishment of provisional MRLs in the EU, which expired on 1.1.2001. The CVMP noted very similar deficiencies in the dossier put forward by the JECFA.

36. In the present situation it is not possible to calculate MRLs, due to a severe lack of reliable data. It is, therefore, also not possible to check whether the MRLs established by JECFA result in a violation of the ADI of 2.5 µg/kg bw/day (= 150 µg/person/day)

37. Given the lack of information on the ratio of marker to total, it is not possible to support the marker residue defined by the JECFA (i.e. sum of thiamphenicol and thiamphenicol conjugates, measured as thiamphenicol). Likewise, there may even be insufficient ground for the marker residue initially proposed by the CVMP (i.e. the parent compound).

38. The CVMP recommended not supporting the draft CCRVDF MRLs.

INTERNATIONAL FEDERATION FOR ANIMAL HEALTH (IFAH)

Porcine Somatotropin

39. IFAH supports the fact that JECFA evaluations and findings are based on sound science and are independent in nature. With the increasing pressures being placed on Codex delegations because of the international trade implications of Codex decisions, the scientific content of the JECFA committee meetings is often subjugated by predetermined positions. This makes the independent scientific nature of JECFA findings even more important.

40. It is perceived that it has become common in the Codex Committee meetings, for some parties, to block the progress of certain products that do not fit their philosophy on animal production and welfare. IFAH wishes to highlight that the setting of Codex MRL standards does not necessarily mean that a product has to be used or registered globally. Individual countries still have the option to regulate the use of a product internally if it does not fit their methods of animal production. For those countries where the use of a product does fit their animal production systems, IFAH believes that they should not be penalized by the lack of an official MRL when the product has been evaluated by JECFA and they have concluded that the product has minimal human safety concerns. IFAH is concerned that the situation for porcine somatotropin is especially troubling in that JECFA reported a “large margin of safety for consumption of residues in food” and that the presence of drug residues “does not present a health concern”. If porcine somatotropin, which does not represent any health concerns and may confer health and other benefits from leaner pork fails to progress at the next CCRVDF meeting, then Codex will not achieve its role of setting food safety standards that protect consumer health and do not unnecessarily hinder trade in animal products.

41. During the twelfth session of CCRVDF in March 2000, the proposed draft MRL’s for porcine somatotropin were advanced to step 5 with the understanding that their further advancement was subject to the outcome of discussion on “other legitimate factors” by the Codex Committee on General Principles. It is

our understanding that the outcome of this discussion did not preclude the use of porcine somatotropin under the definition of Good Veterinary Practice. As the conditions of advancement have been satisfied, IFAH's opinion is that there should be no further delay in the setting of official MRLs for porcine somatotropin.

PART 2: UNSOLICITED COMMENTS SUBMITTED ON DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS RETAINED AT STEP 7 AS LISTED IN ALINORM 01/31, APPENDIX IV

CUBA

42. We agree with what is established in Appendix IV of ALINORM 01/31.

UNITED STATES

Abamectin

43. The U.S. supports advancement of these MRLs. We support the use of the JMPR-derived ADI for Abamectin. We support JECFA's conclusion that the veterinary drug residue definition should not include the photodegradation isomer.

Carazolol

44. The US concurs with JECFA that consumption of injection site tissue 2-hours after treatment would result in an exposure in excess of the acute reference dose (RfD). The U. S. recognizes that the proposed draft "Guidelines for Residues at Injection Sites" will provide member countries with advice on appropriate measures to ensure residues at an injection site do not exceed the acute RfD. The U. S. would support advancement of these MRLs conditional upon the finalization of the Guidelines for Residues at Injection Sites.

Chlotetracycline/Oxytetracycline/Tetracycline

45. The U.S. supports advancement of these MRLs for cattle, pigs, sheep, poultry and milk and the TMRL for fish based on the Committee's decision at the 12th meeting. The U.S. is not aware of any scientific information that would call into question the JECFA safety assessment of these tetracycline antibiotics.

Cyfluthrin

46. The U.S. supports advancement of these MRLs based on the Committee's decision at the 12th meeting. The U.S. agrees with JECFA's conclusion that the inclined plane test results lack the scientific strength needed to form the basis for an ADI. The JECFA ADI was derived from a chronic study and based on decreased body weight gain. This should provide adequate public health protection from the potential neurotoxic effects of this substance, which occurred in test animals at higher doses.

Eprinomectin

47. The U.S. supports advancement of these MRLs based on the Committee's decision at the 12th meeting. The U.S. agrees with JECFA's determination that the CF-1 mouse exhibits a unique sensitivity to the toxic effects of this compound by a mechanism that is not relevant to humans. Therefore, it is not an appropriate model for use in the human food safety assessment of this compound.

Flumequine

48. The U.S. supports advancement of these MRLs based on the Committee's decision at the 12th meeting. The U.S. accepts the basis for JECFA's decision to derive the ADI from toxicological properties of the drug, not microbiological.

EUROPEAN COMMUNITY

49. The 12th meeting of CCRVDF in March 2000, where the European Community objected to draft MRLs for a number of substances, requested the European Community to provide scientific justifications for its positions. These justifications are now provided for cyfluthrin, eprinomectin and flumequine.

Cyfluthrin

50. The study in rats chosen for the determination of the No-Effect-Level (NOEL) cannot be recognized, as changes in haematological parameters were seen at all dose levels. Furthermore, recent data on pharmacological and neurotoxicological effects of cyfluthrin (barbiturate sleeping time in mice and locomotor activity) have revealed effects at lower doses than the NOEL proposed by JECFA. Nevertheless, given that the proposed Codex MRLs are at step 4, the European Community does not oppose the advancement at this stage, but presents concerns regarding the evaluation of this substance and requests a re-evaluation. The European Community would object the advancement of the proposed MRLs to step 8, unless their comments would have been considered and satisfactorily addressed.

Comparison EU (CVMP)/draft CCRVDF (JECFA/JMPR) MRLs

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs (µg/kg)				
				Muscle	Fat	Liver	Kidney	Milk
EU (CVMP)	3 µg/kg bw	Cyfluthrin	Bovine	10	50	10	10	20
Draft CCRVDF (JECFA/ JMPR)	20 µg/kg bw	Cyfluthrin	Bovine	20	200	20	20	40

51. An ADI of 3 µg/kg bw was established by the **CVMP** based on the NOEL of 0.3 mg/kg bw for the prolongation of barbiturate sleeping time in mice and a safety factor of 100. The marker residue has been set as the sum of the 4-cyfluthrin diasteromers. Tissue distribution of cyfluthrin has been taken into account with fat being the major target tissue.

52. The proposed Codex MRLs are based on the ADI established by the **JMPR** for the pesticidal use of the substance. The ADI of 20 µg/kg bw is based on the NOEL of 2 mg/kg bw/day derived from a 2-year oral toxicity study in rats using a safety factor of 100.

53. The CVMP has concerns regarding the ADI and the MRLs proposed. It is recommended that JECFA/JMPR should review the ADI and proposed MRLs in the light of the comments below.

54. The study chosen as pivotal study for the determination of the ADI does not appear appropriate:

- The NOEL derived from the rat study cannot be recognised. In this study rats were exposed to 0, 50, 150 and 450 mg cyfluthrin/kg feed (equal to 0, 2, 8 and 25 mg/kg bw in females and 0, 2, 6, 19 mg/kg bw in males). Data show that the 2 high dose levels resulted in dose-dependent weight gain retardation, but at all dose levels various haematological parameters were changed (e.g. serum glucose levels and haemoglobin concentrations).
- There is evidence from pharmacological data and recent acute neurotoxicity investigations that specific effects of cyfluthrin or ß-cyfluthrin may occur at lower doses, especially when vehicles mimicking fat/water emulsions are used. Thus, the pharmacodynamic effects of cyfluthrin (2% cremophor) include prolongation of barbiturate sleeping time in mice (0.1/0.3/1.0 mg/kg bw) at a dose of 1 mg/kg bw (NOEL 0.3 mg/kg bw. Neurotoxicity investigations revealed effects on locomotor activity at single doses via gavage and cremophor (LOEL of 0.5 mg/kg bw).

55. However, considering that cyfluthrin is currently at step 4, it is proposed that at this time point the European Community does not oppose the advancing of proposed Codex MRLs. Instead, it is proposed that

the concerns would be presented to Codex, and that JECFA/JMPR be asked to review their evaluation, and to comment on the concerns expressed and questions raised. It is proposed that the EU should state that they would object to the advancing of the proposed Codex MRLs to step 8, unless their comments would have been considered and satisfactorily addressed.

Eprinomectin

56. Having reconsidered the assessment made by JECFA, it can be concluded that the MRLs proposed by Codex do not differ significantly from those adopted by the European Community in accordance with Council Regulation (EEC) No 2377/90 and do not pose any risks with respect to consumer safety. The European Community can accept the draft Codex MRLs for eprinomectin.

Comparison EU (CVMP)/draft CCRVDF (JECFA) MRLs

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs (µg/kg)				
				Muscle	Fat	Liver	Kidney	Milk
EU (CVMP)	5 µg/kg bw	Eprinomectin B1a	Bovine	50	250	1500	300	20
Draft CCRVDF (JECFA)	10 µg/kg bw	Eprinomectin B1a	Bovine	100	250	2000	300	20

57. Having re-considered the assessment of the JECFA, it can be concluded that the draft CCRVDF (JECFA) MRLs do virtually provide the same degree of consumer safety as the EU/CVMP MRLs. Therefore, the CVMP recommends to support the draft CCRVDF MRLs.

58. Detailed scientific explanations can be provided, if requested.

Flumequine

59. The European Community expresses its concerns relating to the ADI and the MRLs proposed by JECFA. The toxicological ADI chosen is substantially higher than the microbiological ADI established in the European Community, which is based on data on the most sensitive predominant micro-organism (*E. coli*). Furthermore, taking into account the different ratios of marker to total residues, the European ADI would be exceeded to a varying degree in different species. The only exception in this respect is the species trout. Therefore, the European Community continues not to support the draft Codex MRLs for flumequine, with the exception of that proposed for trout, which is acceptable.

Comparison EU (CVMP)/draft CCRVDF (JECFA) MRLs

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs (µg/kg)				
				Muscle	Fat	Liver	Kidney	Milk
EU (CVMP)	8.25 µg/kg bw (microbiological)	Flumequine	Bovine	200	300	500	1500	50
			Ovine, porcine,	200	300	500	1500	None N/A
			Chicken	400	250	800	1000	N/A
			Turkey	400	250	800	1000	N/A
			Trout	600[1]				N/A
Draft CRVDF (JECFA)	0-30 µg/kg bw (toxicological)	Flumequine	Bovine, ovine, porcine, chicken	500	1000	500	3000	None
			Trout	500[1]				N/A

[1]muscle/skin in natural proportions

60. The **CVMP** established a microbiological ADI of 8.25 µg/kg bw based on the lowest MIC_{50} (0.33 µg/ml) for the most sensitive predominant micro-organism (*E. coli*). This microbiological ADI, being lower than the toxicological one, was adopted for the calculation of MRLs.

61. The **JECFA** established a higher microbiological ADI for flumequine based on the MIC_{50} of the most predominant species in human gut flora, i.e. *Fusobacterium*. In this case the toxicological ADI (rounded up to 30 µg/kg bw) led to a lower ADI and was therefore adopted by the JECFA for the calculation of MRLs. It is also noted that JECFA MRLs do not follow the residue distribution.

62. The ADI proposed as basis for the establishment of CCRVDF MRLs is a toxicological ADI, based on the NOEL of 25 mg/kg bw/day for hepatotoxicity in a 3-month study in mice and a safety factor of 1000. This high safety factor was chosen to reflect the short duration of the study and the lack of histo-chemical characterization of the foci of altered hepatocytes.. However, for this compound the most sensitive parameter to be considered should be the microbiological effects. Using the lowest MIC_{50} (0.33 µg/ml) for the most sensitive predominant micro-organism (*E. coli*) a microbiological ADI of 8.25 µg/kg bw can be calculated. This ADI is lower than the toxicological one proposed and should, therefore, be retained as the basis for the establishment of the MRLs. The difference reported for the microbiological ADI established by the CVMP and the JECFA is due to a different MIC_{50} and to the value given to the daily faecal bolus (150 ml versus 220 ml) (see paragraph 13, CVMP Summary Report, EMEA/MRL/624/99-FINAL, July 1999).

63. Taking into account the ratio of marker to total residues, which differs in the different animal species, and the residues in milk, the microbiological ADI would be exceeded by different amounts in different species which cannot be accepted. This comment does not apply for the MRL for trout.

64. Furthermore, it should be noted that the approach to establish microbiological ADIs is currently under review in the EU, which is likely to influence the assessment in another review of the substance in the future. In addition the ongoing harmonization activities, particularly within the VICH process, will influence the assessment of microbiological safety.

65. The differences between CVMP MRLs and JECFA MRLs are mainly due to the difference in the ADI established, particularly being the difference in the assessment of the microbiological effects. The use of JECFA MRLs would mean that 96% of the ADI of 8.25 µg/kg bw is used in the case of cattle and chicken and it is not possible to establish an MRL for cow's milk anymore. Furthermore, the use of JECFA MRLs for pigs would lead to exceeding the microbiological ADI with 24%.

66. Therefore, the CVMP recommended continuing not to support the draft CCRVDF (JECFA) MRLs, with the exception of the MRL for trout. The draft CCRVDF MRL for trout is considered acceptable.