codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Viale delle Terme di Caracalla 00100 ROME Tel: 39 06 57051 www.codexalimentarius.net Email: codex@fao.org Facsimile: 39 06 5705 4593

Agenda Item 5 **CX/RVDF 01/5**
November 2001

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS
Thirteenth Session
Charleston, South Carolina, USA, 4-7 December 2001

CONSIDERATION OF PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS AT STEP 4

PART 1: COMMENTS SUBMITTED AT STEP 3 IN RESPONSE TO CL 2001/28-RVDF ON THE PROPOSED DRAFT MAXIMUM RESIDUE LIMITS RECOMMENDED BY THE 54TH MEETING OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

BRAZIL

1. Brazil supports the maintenance at step 3 considering the specific considerations of the medicines Cyhalothrin, Dicyclanil, Ivermectin, Lincomycin, Melengestrol Acetate and Trichlorfon (Metrifonate).

FINLAND

Cyhalothrin

2. The MRLs for bovine tissues and milk can be supported. The proposed MRLs for pigs and sheep cannot be supported because the marker residue in these species is unknown.

Dicyclanil

3. The proposal cannot be supported because the maximum daily intake based on the proposal would amount to approximately 240% of the ADI.

Ivermectin

4. No MRL for milk has been applied in the EU. No information is available to precisely calculate the residue intake from milk. The proposal cannot be supported.

Lincomycin

5. The proposed MRL can be supported.

Melengestrol Acetate

6. No comment.

Trichlorfon

7. In absence of sufficient information on the toxicological and residue profile of this substance the proposal cannot be supported.

HAITI

8. No comments.

SPAIN

Cyhalothrin

9. No comment.

Dicyclanil

10. We propose the following MRLs:

SPECIES	TISSUE	MRL (µg/kg)
Sheep	Fat	50

Lincomycin

11. We propose the following MRLs:

SPECIES	TISSUE	MRL (µg/kg)
Cattle	Fat	50
Pig	Fat	50
Sheep	Fat	50
Chicken	Fat	50

Melengestrol Acetate

12. No comment.

TURKEY

13. No comment.

UNITED STATES

Cyhalothrin

14. The U.S. supports all the proposed TMRLs. Outstanding toxicology and residue issues will be addressed at the 58th meeting of JECFA (February, 2002).

Dicyclanil

15. U.S. supports the MRLs recommended by JECFA. The US supports advancement of Dicyclanil to step 5/8 of the procedure, with omission of steps 6 & 7, for the following reasons: it is used in all major sheep-producing countries around the world; the MRLs and ADI are final; and no country has approved MRLs higher than those recommended by JECFA.

Ivermectin

16. U.S. supports this TMRL for cattle milk. The U.S. and JECFA ADI are identical and the TMDI does not exceed the ADI.

Lincomycin

17. The U.S. supports advancement of these TMRLs for cattle, sheep and chicken and MRLs for pigs and cattle milk.

Melengestrol Acetate

18. U.S. supports the advancement of these TMRLs. The U.S. has determined that when used in accordance with good veterinary practice, residues of MGA are safe for human consumption.

Trichlorfon

19. The U.S. supports advancement of this MRL for trichlorfon in milk. The U.S. is not aware of any scientific information that would call into question JECFA's safety assessment of trichlorfon.

EUROPEAN COMMUNITY

Cyhalothrin

20. It is recommended to accept the proposed draft Codex MRLS for cyhalothrin in bovine and ovine species 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.

21. The European Community does not give the support for the proposed Codex MRLs for cyhalothrin for porcine tissues at present, as the ratio of marker to total residues can not be determined due to a lack of adequate studies.[1]

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

	ADI	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)				
				Muscle	Fat	Liver	Kidney	Milk
EU (CVMP)	5 µg/kg bw	Bovine	Cyhalothrin (sum of isomers)	---	500	---	50	50
		Porcine		---	---	---	---	---
		Ovine		---	---	---	---	---
Draft CCRVDF (JECFA)	0-2 µg/kg bw*	Bovine	Cyhalothrin	20	400	20	20	30
		Porcine		20	400	20	20	N/A
		Ovine		20	400	20**	20	---

* Results of appropriate studies to establish a NOEL for neurobehavioural effects in laboratory animals are required for evaluation in 2002
****** Results of the validation of the analytical method to demonstrate a limit of quantification of 0.01 mg/kg (sheep liver) are required for evaluation in 2002.

22. The **CVMP** established a toxicological ADI of 5 µg/kg bw/day based on a NOEL of 0.5 mg/kg bw applying a safety factor of 100. The NOEL is based on a 52-week oral study in Beagle dogs, with

[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 Commission 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).

administration of cyhalothrin in corn oil by gelatine capsules - neurological signs: muscular trembling, unsteadiness and vomiting. The safety factor was considered justified because the toxicity study was conducted with a suitable lipophilic vehicle.

23. The **JECFA** established an ADI of 2 µg/kg bw/day (120µg per person) based on a LOEL for induction of liquid faeces in a 26-week study in dogs. A safety factor of 500 was used, because of the absence of a NOEL for liquid faeces in dogs and because of the absence of a NOEL for neurobehavioral effects. The JECFA ADI is temporary and new studies to establish a NOEL for neurobehavioural effects in laboratory animals have been requested.

24. The **CVMP** identified cyhalothrin as marker residue in cattle. From the results of the different radiometric studies, it was estimated that cyhalothrin represents 100% of the total residues in muscle and fat, 20% in kidney and 90% in milk. In absence of radiolabelled studies in ovine and swine, no marker residue could be identified for the species. No method was available for monitoring residues of cyhalothrin in ovine milk and swine tissues.

25. No depletion studies using radiolabelled cyhalothrin were reported by the **JECFA** in any species. The JECFA claims to have suitable analytical methods validated for the edible tissues of the three species (bovine, ovine and swine), although the method in ovine liver has only a temporary status for validation. References for the validated analytical method in swine are scarce.

26. It is not possible to judge if the evaluation made by JECFA experts was based on the same studies that were available to CVMP.

27. The **JECFA** proposed for cyhalothrin temporary MRLs until 2002, until more toxicological results and a validated analytical method for ovine liver are presented. The same temporary MRLs are used for edible tissues from animal origin of cattle, pigs and sheep, and relating to the analytical method, it is stated that: (A) a suitable analytical method is available for analysis of cyhalothrin residues in edible tissues and milk. (B) MRLs for liver, kidney and muscle can be harmonized at twice the LOQ of the analytical method as validated for tissues from cattle and pigs. (C) MRLs for fat are based on the highest mean residues, plus 3 standard deviations, as determined in depletion studies using treatments consistent with good practice in the use of veterinary drugs. (D) The MRL recommended for milk is based on the highest mean residues, plus 3 standard deviations, as determined in depletion studies which used treatments with the spray formulation consistent with good practice in the use of veterinary drugs.

28. Based on the consumption of the international animal food basket, and with the marker to total residue ratio (liver: 1/16 and kidney 1/5, with the others as 1/1), the TMDI is 108 µg. The remainder of the ADI (12 µg) has been allocated to pesticide use.

29. Regarding the allocation of the ADI to residues from use as pesticide and veterinary drug, the **JECFA** proposed a TMDI of 108 µg (90%) for residues of animal origin and 12 µg (10%) for residues of vegetable origin.

30. While the ovine MRLs can in principle be supported provided that a validated analytical method can be made available before the proposed MRLs would be advanced to step 7, the CVMP recommended not supporting the proposed draft CCRVDF MRLs in porcine species.

31. The reasons are that no radiolabelled depletion study is available for pigs, which does not allow to identify the marker residue in pigs, and the analytical method does not seem to be fully validated. Without data on these two points it is not possible to support approval of MRL values in pigs.

32. Furthermore, it should be noted that cyhalothrin MRLs are still under review in the EU and further comments may arise in the future.

Dicyclanil

33. The European Community cannot give support to the proposed draft Codex MRLs for dicyclanil, as the use of dicyclanil itself as a marker gives an estimated total maximum daily intake far above the ADI (330%).

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

	ADI	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)			
				Muscle	Fat	Liver	Kidney
EU (CVMP)	7 µg/kg bw	Ovine	Sum of dicyclanil and 2,4,6-triamino-pyrimidine-5-carbonitrile	200	150	400	400
Draft CCRVDF (JECFA)	0-7 µg/kg bw	Ovine	Dicyclanil	200	150	400	400

34. JECFA and CVMP ADIs are identical and are based on the same data and approach. The ADI of 0.007 mg/kg bw (0.42 mg per person) was based on a NOEL of 0.7 mg/kg bw/day observed in a 12-month dietary toxicity study in dogs and a safety factor of 100.

35. Numerical figures for the MRLs are identical. However, the JECFA and CVMP approaches differ in the definition of the marker residue: CVMP MRLs refer to the sum of dicyclanil and the major metabolite 2,4,6-triamino-pyrimidine-5-carbonitrile while the JECFA has proposed the parent compound alone as the marker residue.

36. The tissue distribution of the two components of the CVMP marker residue may be described as follows: The metabolite 2,4,6-triamino-pyrimidine-5-carbonitrile was present in all tissues and represented the dominant residue fraction in liver and kidney, while parent compound predominated in fat. In muscle, both parent compound and 2,4,6-triamino-pyrimidine-5-carbonitrile were present in comparable amounts (see CVMP document EMEA/MRL/739/00-Final of May 2000).

37. Due to the difference in the marker residue between JECFA and CVMP, the ratios marker to total residues were also different: The ratio for parent dicyclanil to the total residues is lower (equal, at most) than that for the sum of parent dicyclanil plus the major metabolite. This difference in ratios was most noticeable in kidney, liver and muscle. Accordingly, a much larger correction factor was needed to estimate the theoretical maximum total residue intake (TMDI) resulting from JECFA MRLs. In consequence, JECFA MRLs, although numerically identical to CVMP MRLs, would lead to a higher residue intake.

38. The theoretical maximum daily intake (TMDI) calculated on the basis of the CVMP marker "sum of dicyclanil and 2,4,6-triamino-pyrimidine-5-carbonitrile" already represented about 100 % (> 98 %) of the ADI (see CVMP Summary Report EMEA/MRL/739/00-Final of May 2000). An estimate of the TMDI on the basis of the JECFA marker and its ratio to total residues showed that total residue intake would exceed the ADI by a factor of more than 3 (332.6 % of the ADI, see Annex 1).

39. In conclusion, use of the JECFA marker "parent dicyclanil" would lead to an unacceptable exceedance of the ADI of 0.42 mg/person by the theoretical maximum daily residue intake.

40. Therefore the CVMP recommended not supporting the proposed draft CCRVDF MRLs.

Theoretical maximum daily intake of residues (TMDI)
(estimated on the basis of the marker residue "Sum of Dicyclanil plus 2,4,6-triamino-pyrimidine-5-carbonitrile" (CVMP) and for the marker "Dicyclanil" (JECFA)

Tissue	Cf = consumption factor (kg)	**MRL (µg/kg)**	**CVMP marker residue % ratio marker/total residues [1)]**	**JECFA marker residue % ratio marker/total residues [2)]**
Liver	0.1	400	15	4.5
Fat	0.05	150	100	92.3
Kidney	0.05	400	25	6.25
Muscle	0.3	200	100	33.3
			TMDI = 414.2 µg (98.6 % of ADI)	**TMDI = 1397.2 µg (332.6 % of ADI)**

$TMDI_{food\ basket} = \sum MRL_{tissue} \times 100/(\%\ ratio\ marker/total)_{tissue} \times Cf_{tissue}$

[1)] Ratios for the sum of dicyclanil and 2,4,6-triamino-pyrimidine-5-carbonitrile as stated in the CVMP Summary Report EMEA/MRL/739/00-Final
[2)] Estimated from the ratios for the sum of dicyclanil and 2,4,6-triamino-pyrimidine-5-carbonitrile as stated in the CVMP Summary Report EMEA/MRL/739/00-Final and individual results for determinations of dicyclanil and of 2,4,6-triamino-pyrimidine-5-carbonitrile

Ivermectin

41. The European Community cannot give the support for the proposed draft Codex MRL for ivermectin for milk at present, as no information is available on the ratio of marker to total residues, which gives an unacceptable uncertainty to the estimation of the theoretical maximum daily intake.[1]

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

	ADI	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)				
				Muscle	Fat	Liver	Kidney	Milk
EU (CVMP)	1 µg/kg bw	Bovine	22,23-Dihydro-avermectin B1a	-	40	100	-	-
Draft CCRVDF (JECFA)	0-1 µg/kg bw	Bovine*	22,23-Dihydroaver-mectin B1a (H2B1a)	-	40✞	100✞	-	10

* Validation data on the analytical method and information on other routes of applications to cattle to evaluate the residues in milk are required for evaluation in 2002
✞ Tissue MRLs were already previously established by JECFA, under discussion is the milk MRL.

42. The CVMP and the JECFA established the same ADI and MRLs for bovine tissues including values for fat and liver. Recently, the CVMP set MRLs for all edible tissues in deer leading to a maximum daily intake of 87% of the ADI. No MRL has been set in the EU for milk. Codex proposes now to set an MRL for milk at 10 µg/kg. Thus there is a concern that addition of an MRL for milk will result in a daily residue intake, which may exceed the ADI.

43. No information is available on the ratio of marker residue to total residues to calculate the ivermectin residue intake from milk. However, considering a ratio of 1 or 0.5 maximum daily residue intakes will amount 112% respective 137% of the ADI (see table).

	Daily residue intake [µg/person]	
Tissues	52	52
Milk (ratio 1)	15	
Milk (ratio 0.5)		30
Total	67	82
% of ADI	112	137

44. The CVMP therefore recommended not supporting the proposed CCRVDF MRL.

Lincomycin

45. It is recommended to accept the proposed draft Codex MRLS for lincomycin 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.

Melengestrol Acetate

46. The European Community cannot give support for the proposed draft MRLs for melengestrol acetate as no safety and residue evaluation has been performed in the European Community, as no application was submitted.

Trichlorfon

47. The European Community does not give the support for the proposed draft Codex MRLs for trichlorfon (metrifonate) for porcine tissues for the following reasons: Severe safety concerns are expressed in view of the substance being clearly fetotoxic, teratogenic and mutagenic. There is also convincing data on congenital effects in humans. The proposed ADI is furthermore based on a totally inappropriate study on acute effects in a diseased human sub-population (patients with Alzheimer disease).[1]

48. The **JECFA** set an ADI of 0-20 µg/kg bw and recommended an MRL for bovine milk of 50 µg/l. MRLs were not recommended for muscle, liver, kidney or fat in cattle considering that no detectable residues should be present in tissues from animals treated with trichlorfon when used in accordance with good practice in the use of veterinary drugs. The limit of quantification may be used as a guideline maximum residue concentration in muscle, liver, kidney and fat (50 µg/kg).

49. The **CVMP** assessed trichlorfon (metrifonate) in 1999 but concluded that it was not possible to establish MRLs.

50. In its evaluation, the **JECFA** concluded that inhibition of acetylcholinesterase activity was the most relevant endpoint for establishing an ADI. The most appropriate NOEL was 0.2 mg/kg bw per day for inhibition of erythrocyte acetylcholinesterase activity in humans treated orally. A safety factor of 10 was applied to this figure, giving an ADI of 0-20 µg/kg bw.

51. The CVMP could not establish an ADI due to the concerns regarding pharmacokinetics, teratogenicity, mutagenicity and neurotoxicity of the substance, and which are described below.

52. Differences in pharmacokinetics between laboratory animals and humans comprise orders of magnitude. Generally, the pharmacokinetics of metrifonate in rodents and other laboratory animals appear to differ substantially from that observed in humans. Therefore, effects in humans may be expected at trichlorfon doses, which are lower by several orders of magnitude, than that inducing the corresponding effects in laboratory species.

53. Trichlorfon is clearly fetotoxic and teratogenic in a number of laboratory species. Whereas NOELs for developmental toxicity could be identified in the mouse (~300 mg/kg bw, p.o.), rat (50 mg/kg bw, p.o.), hamster (200 mg/kg bw, p.o.), and rabbit (45 mg/kg bw, p.o.), severe teratogenic effects without NOELs were observed in guinea pigs and pigs.

54. In guinea pigs, oral doses of 100 mg/kg bw for 6 days at mid-gestation caused reduced brain weight with altered morphology and biochemistry resulting in locomotor disturbances in the offspring. No NOEL was established. In pigs, offspring of sows treated with daily doses of 40-100mg/kg bw for one to three days during mid gestation were observed to show congenital tremor with cerebral, predominantly cerebellar hypoplasia and loss of Purkinje cells. Again, a NOEL was not established. No explanation was given as to why JECFA dismissed the effects in these two species.

55. The JECFA concluded that since the tests conducted *in vivo* produced mostly negative results when trichlorfon is administered orally, that the weight of evidence indicates that it is unlikely to represent a genotoxic risk. A 'weight of evidence' approach is often very subjective. In the case of trichlorfon, 20/33 in vitro studies and 4/9 in vivo investigations gave positive finding (see Annex 2). Trichlorfon is clearly genotoxic *in vitro*.

56. In addition to the 4 positive *in vivo* tests reported by the JECFA there are at least 3 other reports of induction of aneuploidy *in vivo* by trichlorfon that were not included in the JECFA assessment.

57. Czeizel (1994), reported highly statistically significant increases ($p<0.001$) in peripheral lymphocytes of 5 humans who attempted suicide by ingesting a trichlorfon-based pesticide. A similar highly significant increase was still present at 180 days in the 4 survivors.

58. Tian et al. (2000) reported high frequencies of micronuclei, mosaic aneuploidys and developmental retardation in embryos of pregnant female mice exposed to an acute i.p. dose of trichlorfon at 6 hr post presumed conception.

59. Sun et al. (2000) investigated spindle disturbances in vitro and effects on male germ cells *in vivo*. *In vitro*, trichlorfon (40-120 µg/ml) was a potent spindle poison in V79 cells. There was a dose-related increase in mitoses with spindle disturbances (>20-fold higher than controls at 120 µg/ml. In an *in vivo* FISH assay, single i.p. doses of 200-405 mg trichlorfon/kg bw caused a dose-dependent increase in disomic sperm.

60. Furthermore, dichlorvos to which trichlorfon is transformed, is mutagenic at the site of contact and no data are available to investigate this for trichlorfon. This is a particular cause for concern as trichlorfon is used topically and ingested residues in skin/fat/muscle are unlikely to have been extensively metabolised. The carcinogenicity studies on trichlorfon were also equivocal. There is also a convincing report of congenital effects in humans. A case-control study of a cluster of congenital abnormalities in a small Hungarian village found an association between ingestion of trichlorfon-contaminated fish and an increase of Down's syndrome cases, other malformations and twins. The Down's cases suggest a link between effects observed in laboratory species.

61. In the **CVMP** assessment, delayed neurotoxicity was observed in hens and primates ant toxic doses. Delayed neurotoxicity is regarded as a non-threshold effect by the CVMP. Again, there is no information why JECFA dismissed these data.

62. The **CVMP** were unable to set an ADI due to the concerns listed above. The **JECFA** set an ADI based on a NOEL from a prospective, double-blind, randomised clinical trail of trichlorfon in Alzheimer patients. Four groups of patients received daily oral doses at an initial loading dose of 0, 0.5, 0.9 or 2.0 mg/kg bw for two weeks in order to achieve steady-state cholinesterase inhibition quickly. This was followed by eight weeks of daily doses of 0, 0.2, 0.3 or 0.65 mg/kg bw daily. The intermediate and high doses improve cognitive function; the low dose had equivocal effects. Side effects were most severe in the high dose. The initial low dose of 0.5 mg/kg bw inhibited erythrocyte acetylcholinesterase by 29% and subsequent administration of 0.2 mg/kg bw maintained inhibition at 30-37%. The JECFA considered that as this dose enhanced inhibition by only 8% an insignificant change, 0.2 mg/kg bw was the NOEL for acetylcholinesterase inhibition.

63. The low dose was not a NOEL. Irrespective of the effects on cholinesterase, there were equivocal clinical effect (and side-effects) at this dose. At best it can be regarded as a LOEL, which required an additional uncertainty factor to determine an ADI.

64. The derivation of a N(L)OEL of 0.2 mg trichlorfon/kg bw in human patients from a small increase of AChE inhibition after the reduction of 0.5 mg/kg bw loading dose to 0.2 mg/kg bw maintenance dose appears not based on sound scientific considerations. It is wholly inappropriate to base an ADI on a LOEL from clinical trail data involving a diseased sub/set of an aged sub-group of the human population.

65. Considering the severe safety concerns outlined above the CVMP strongly recommended not supporting the establishment of MRLs for trichlorfon.

Summary of mutagenicity data (JECFA)

Study	Endpoint	Dose	Result	Reference
In vitro Interaction with DNA	7-methylguanine in mouse urine	160 mg/kg i.p.	Positive	Dedek *et al.* (1976)
	7-methylguanine in mouse liver and kidney	120 mg/kg i.p.	Positive	Dedek (1971)
Gene mutation (*rec*)	*B. subtilis* NIG17, 45	0.3 mg/disc-S9	Negative	Inukai & Iyatomi (1977)
	P. mirabilis PG273, 713	10 mg/spot-S9	Positive	Alder *et al.* (1976)
	B. subtilis H17, M45	NR-S9	Negative	Shirasu *et al.* (1976)
	B. subtilis H17, M45	2 mg/disc-S9	Positive	Shirasu *et al.* (1979)
	S. typhimurium	10 mg/disc	Positive	Jones *et al.* (1984)
Reverse mutation	*S .typhimurium* TA100, 98, 1535, 1538	5 mg/plate ± S9	Positive (TA 100 only)	Byeon *et al.* (1976)
	TA98, 100, 1535, 1537	0.5 mg/plate ± S9	Negative	Inukai & Iyatomi (1977)
	TA98, 100	~8.5 mg/plate ± S9	Positive	Batzinger & Bueding (1977)
	TA100, 1535	10 mg/plate ± S9	Negative	Zeiger *et al.* (1987)
	TA98, 100	2 mg/plate ± S9	Negative	Diril *et al.* (1990)
	TA1535, 1536, 1537, 1538 *E. coli* WP2/WP2*hcr*	NR-S9	Negative	Shirasu *et al.* (1976)
	TA1535, 1536, 1537, 1538	2 mg/disc -S9	Negative	Carere *et al.* (1978a/b)
	TA98, 100, 1535, 1537, 1538 *E. coli* WP2*hcr*	20 mg/plate ± S9	Positive (TA100, *E.coli*)	Shirasu *et al.* (1979) Moriya *et al.* (1983)
	TA97, 98, 100, 104, 1535	25 mg/plate ± S9	Positive (TA100, 104)	Barrueco *et al.* (1991)
	TA98, 100, 1535, 1537 *E. coli* WP2*uvrA*	5 mg/plate ± S9	Positive (except TA98, 1537)	Watabe (1997)
	S. cerevisiae 632/4, 632/1b, 814/18b	NR-S9	Negative	Guerzoni *et al.* (1976)
	S. cerevisiae S138, S211a	10 mg/ml ± S9	Negative	Hoorn (1983)
	S. cerevisiae D7	40 mg/ml ± S9	Positive	Jones *et al.* (1984)
Mitotic crossing over, gene conversion	*S. cerevisiae* D7	40 mg/ml ± S9	Positive	Jones *et al.* (1984)
Forward mutation	*S. coelicolor*	2 mg/disc -S9	Positive	Carere *et al.* (1978a/b)
	S. pombe SP-198	30 mg/ml ± S9	Positive	Gilot-Delhalle *et al.* (1983)
	V79 cells	200 mg/ml -S9	Negative	Aquilina *et al.* (1984)
	L5178Y cells	200 µg/ml -S9 600 µg/ml +S9	Positive	Witterland (1984) Jones *et al.* (1984)

DNA damage	*E. coli* pol $^{+/-}$	10 mg/plate ± S9	Negative	Herbold (1984)
	E. coli SOS	NR ± S9	Negative	Xu & Schurr (1990)
UDS	EUE cells	1000 mg/ml -S9	Positive	Aquilina *et al.* (1984)
	1º rat hepatocytes	50 µg/ml -S9	Negative	Myhr (1983)
SCE	V79 cells	80 µg/ml -S9 60 µg/ml +S9	Positive	Chen *et al.* (1981, 1982)
	CHO cells	100 µg/ml -S9 2 mg/ml -S9	Positive	Jones *et al.* (1984) Putman (1987)
Chromosomal damage	Don-6 cells	250 mg/ml -S9	Positive	Sasaki *et al.* (1980)
	Human lymphocytes	30 mg/ml -S9 3000 mg/ml +S9	Positive	Herbold (1986)
In vivo Reverse mutation	Host Mediated assay in mice TA98,100	200 mg/kg p.o.	Positive (TA100)	Batzinger & Bueding (1977)
Recessive lethal	*Drosophila*	4.5 mg/kg	Negative	Benes & Sram (1969) Brzheskiy (1973) Lamb (1977)
SCE	Chinese hamster bone marrow	300 mg/kg p.o.	Negative	Volkner (1987)
Chromosomal damage	Mouse bone marrow micronuclei	2 x 312 mg/kg i.p. 2 x 250 mg/kg p.o. 2 x 400 mg/kg p.o. 400 mg/kg p.o. 400 mg/kg p.o. (+) en 600 mg/kg p.o. (-) en	Positive (-)enantiomer only	Paik & Lee (1987) Herbold (1979a) Jones *et al.* (1984) Herbold (1997)
	Metaphase analysis in mouse bone marrow	400 mg/kg p.o. 10 mg/kg i.p.	Positive	Kurinnyi (1975) Moutschen-Dahmen *et al.* (1975) Degraeve *et al.* (1982, 1984) Nehes *et al.* (1982)
		100 mg/kg i.p. 0.5 mg/ml water (5dy/wk 7wks) 405 mg/kg i.p.	Negative	
	Metaphase analysis in hamster bone marrow	250 mg/kg i.p.	Negative	Dzwonkowska & Hubner (1986)
	Metaphase analysis in rat bone marrow	250 mg/kg p.o.	Negative	Bootman & Hobson-Walker (1987)
	Metaphase analysis in mouse spermatogonia/ Spermatocytes	1.5 mg/ml in water 50-100 days	Positive	Bulsiewicz *et al.* (1976) Moutschen-Dahmen *et al.* (1981) Degraeve *et al.* (1982, 1984) Herbold (1992)
		100 mg/kg bw i.p. 0.5 mg/ml water (5dy/wk 7 wks) 100 mg/kg i.p.	Negative	
	Dominant lethal mutation in mice	100 mg/kg i.p. 0.5 mg/ml water (5dy/wk 7 wks) 280 mg/kg i.p. 405 mg/kg i.p. 250 mg/kg p.o. NR	Negative	Estein *et al.* (1972) Dedek *et al.* (1975) Fischer *et al.* (1977) Herbold (1979b,c) Becker & Schoneich (1980) Moutschen-Dahmen *et al.* (1981) Degraeve *et al.* (1982, 1984) WHO (1992)
		405 mg/kg i.p. 405 mg/kg i.p. 54 mg/kg i.p. 3 weeks	Positive	

PART 2: UNSOLICITED COMMENTS SUBMITTED ON PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS RETAINED AT STEP 4 AS LISTED IN ALINORM 01/31, APPENDIX VI

CUBA

66. We agree with what is established in Appendix VI of ALINORM 01/31.

UNITED STATES

Clenbuterol (cattle tissues)

67. The U.S. has concerns about the abuse potential associated with this drug and the documented risk to the public health from its use as a growth-promoting agent. The U.S. could support Codex MRLs for clenbuterol in cattle tissue as a means to distinguish between residues caused by therapeutic use (e.g., as a tocolytic agent) vs. residues caused by illegal/inappropriate use as a growth-promoting agent.

Deltamethrin

68. The U.S. supports these MRLs 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 JECFA's safety assessment of deltamethrin.

EUROPEAN COMMUNITY

Deltamethrin

69. The European Community has concerns that the estimated daily intake from veterinary drug residues and pesticidal residues would result in the ADI being exceeded with the proposed Codex MRLs (114%). Nevertheless, the European Community does not oppose the advancement of the process at this stage, but presents concerns regarding the evaluation of this substance and requests a reevaluation and a reduction of the MRLs proposed. The European Community would object to 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	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)					
				Muscle	Fat	Liver	Kidney	Milk	Eggs
EU (CVMP)	10 µg/kg bw	Bovine	Deltamethrin	10*	50*	10*	10*	20*	N/A
		Ovine	"	10*	50*	10*	10*	none	N/A
		Chicken	"	10*	50*	10*	10*	N/A	50*
		Fin fish	"	10*					
Draft CCRVDF (JECFA/ JMPR)	10 µg/kg bw	Bovine	Deltamethrin	30#	500	50	50	30#	N/A
		Ovine	"	30#	500	50	50	none	N/A
		Chicken	"	30#	500	50	50	N/A	30#
		Salmon	"	30#					

* Provisional MRLs due to questions on the analytical method.

\# Guidance values at twice the limit of quantification; no residues were measured.

70. While both the **CVMP** and the **JECFA** adopted an ADI of 10 µg/kg bw based on a NOEL of 1 mg/kg bw from long term studies in rats, mice and dogs, the two committees came to different conclusions on setting MRLs for deltamethrin. These appear to have been complicated in both cases by the requirement of both to take into account pre-existing determinations by their respective counterparts involved in assessment of plant protection products, rather than fundamental scientific arguments.

71. In 1990 the **JMPR** established MRLs for deltamethrin as a pesticide, taking into account use as a veterinary drug: 500 µg/kg in meat (fat), 50 µg/kg in offal and 20 µg/kg in milk. The target species were not specified. The **JECFA** took account of these MRLs and recommended the same MRLs for liver, kidney and fat. The JECFA noted that the concentrations of residues in muscle, milk and eggs were less than twice the limit of quantification of the analytical methods used and therefore recommended MRLs based on the sensitivity of the methods. These 'guidance MRLs' were 30 µg/kg for muscle in cattle, sheep, chickens and salmon and for cows' milk and chickens' eggs, expressed as parent drug. These "guidance MRLs" should not be used in determining the TMDI.

72. In 1999 the **CVMP** established MRLs for deltamethrin in animal tissues taking into account those already fixed for pesticidal use by Council Directive 98/82/EC of 50 µg/kg for fat and eggs (the lower limit of determination). Provisional MRLs of 10 µg/kg muscle, liver and kidney, and 20 µg/kg for bovine milk were determined based on the current LOQ of 5 µg/kg.

73. The CVMP MRL values represent a TMDI of about 8% of the ADI, compared to 72% from pesticidal use.

74. As stated above, the principal problem in the differences between the MRLs set by JECFA and CVMP result from the procedural requirement of both to take into account previous pesticidal assessments.

75. One point of confusion noted was that the JMPR MRLs were based on the sum of 3 isomers, cis-deltamethrin, trans-deltamethrin and alpha-3-deltamethrin as the marker residue. This approach was also originally adopted by the JECFA but was not followed by the CVMP, as deltamethrin (cis-deltamethrin) is the only substance present in edible tissues. The JECFA subsequently decided to use deltamethrin as marker residue, but do not appear to have altered the MRLs to take this change into account.

76. Based on the CVMP estimate for intake from pesticidal use, and marker: total residue data from JMPR, the TMDI of deltamethrin equivalents using the MRLs for liver, kidney and fat will amount to 80% using the EU MRLs and 114% using the JECFA values (see table below).

Tissue	**Intake (kg)**	**Marker: Total Ratio**	**CVMP**		**JECFA**	
			MRL	**Residue**	**MRL**	**Residue**
Liver	0.1	0.04	10	25	50	125
Fat	0.05	0.6	50	4.2	500	42
Kidney	0.05	0.03	10	17	50	83
Total Veterinary Intake				46.2		250
Pesticide Intake (72% ADI)				432		432
TMDI (% ADI)				478.2 (80%)		682 (114%)

77. The CVMP has concerns regarding the estimated daily intake of deltamethrin residues, which would result in the ADI be exceeded. However, considering that deltamethrin is currently at step 4, it is proposed that at this time point the EU 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 European Community 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.