codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATIONS OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Viale delle Terme di Caracalla 00100 ROME Tel: +39(06)5701 E-mail: Codex@FAO.org Fax: +39(06)5705.4593

Agenda Item 8 **CX/RVDF 00/08**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS
Twelfth Session
Washington, D.C., 28 – 31 March 2000

CONSIDERATION OF MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS at Steps 7 and 4

(Government Comments)

In response to CL 1999/13-GEN; CL 1999/18-RVDF and ALINORM 99/31 the following comments have been received from governments and interested International Organizations.

Comments at Step 6

No comments were received at Step 6

Comments at Step 3

Comments at Step 3 on proposed draft maximum residue limits for veterinary drugs (MRLVDS) arising from the 52nd meeting of the Joint FAO/WHO Expert Committee on Food Additives were received from Australia, the European Union and Consumers International.

Australia

Australia does not support the advancement of the proposed draft MRLs for deltamethrin in muscle, fat and milk but proposes that they be reviewed in light of the harmonization discussions between JECFA/JMPR so that a uniform approach occurs in Codex to the tissues in which MRLs are set and to the nomenclature used for setting MRLs for fat soluble pesticides.

Australia questions the setting of MRLs in fat for dihydrostreptomycin/streptomycin. This is not a lipophilic compound and therefore it would seem inappropriate to monitor for residues in fat.

Australia supports all other proposed draft MRLs.

European Union

The comments reflect the position of the following delegations:
Belgium, Germany, Denmark, Greece, Spain, Ireland, Italy, Finland, France, Luxembourg, Netherlands, Austria, Portugal and Sweden.

The residue evaluations of JECFA and the EU-CVMP are compared, if possible. Shading highlights differences. If necessary comments are made on the substance or the reasoning for the differences in the evaluation. Finally, the position of the delegations on the substance is summarised.

The following abbreviations are used:

EU = European Community
CVMP = Scientific Committee for Veterinary Medicinal Products of the EU
JECFA = Joint FAO/WHO Expert Committee on Food Additives
ADI = acceptable daily intake
MRL = maximum residue limit
bw = body weight

General Remark:

It has to be emphasised that yet again final report of the proceeding JECFA Meeting (51st session) is again not available before comments on the MRL adopted in this session are to be made. This fact alone should prevent consideration of the proposed MRLs at this time. Consequently only if the results of the EU evaluation and the JECFA evaluation are somewhat similar, it would be considered that the evaluation is based on similar data.

Deltamethrin

	ADI	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)					
				Muscle	Fat	Liver	Kidney	Milk	Eggs
EU	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*
JECFA	0-10 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#	500	50	50	N/A	N/A

* Provisional MRLs due to questions on the analytical method
\# Guidance values at twice the limit of quantification; no residues were measured

The MRLs recommended by the EU-CVMP are the same as those previously adopted by the European Union for pesticide uses of deltamethrin. Therefore, and also taking account of the wide-spread use of deltamethrin as a pesticide on vegetable crops, the EU adopted the EU-Pesticide MRLs, which only lead to a maximum daily intake of around 8% of the ADI.

POSITION: The delegations do **not** support the JECFA/Codex MRLs.

It is also noted that the CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS 11TH SESSION, WASHINGTON DC, 1998 generally recognized the need for harmonization for compounds used both as veterinary drugs and pesticides (paragraph 8,9,11 and 62 of ALINORM 99/31). At the time it requested the FAO Secretaries of the JECFA and JMPR to convene an informal meeting of experts in the areas of residues of veterinary drugs and pesticides to consider these issues. The outcome of this meeting would be reported and considered by the CCRVDF and the CCPR. The delegations have not been informed of the outcome of such a meeting.

Dihydrostreptomycin/Streptomycin

	ADI	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)					
				Muscle	Fat	Liver	Kidney	Milk	Eggs
EU	30 µg/kg bw*	Bovine	Dihydrostreptomycin	500*	500*	500*	1000*	200*	N/A
		Ovine	"	500*	500*	500*	1000*	200*	N/A
		Porcine	"	500*	500*	500*	1000*	N/A	N/A
		Chicken	"	500*	500*	500*	1000*	N/A	50*
EU	30 µg/kg bw*	Bovine	Streptomycin	500*	500*	500*	1000*	200*	N/A
		Ovine	"	500*	500*	500*	1000*	200*	N/A
		Porcine	"	500*	500*	500*	1000*	N/A	N/A
		Chicken	"	500*	500*	500*	1000*	N/A	50*
JECFA	0-50 µg/kg bw	Bovine	Sum of dihydrostrepto-mycin and streptomycin	600#	600#	600#	1000#	200✧	N/A
		Ovine	"	600#	600#	600#	1000#	None	N/A
		Porcine	"	600#	600#	600#	1000#	N/A	N/A
		Chicken	"	600#	600#	600#	1000#	N/A	none

* Provisional ADI and MRLs
\# More sensitive analytical methods are requested by 2001
✧ Temporary MRL until 2001

The EU MRLs are provisional and will expire on 1 June 2000. They will be reconsidered. The EU-CVMP and JECFA set different marker residues. However, the JECFA-MRLs do not much differ from the provisional EU-values.

POSITION: The delegations **may support** the JECFA/Codex MRLs.

Doramectin

To the knowledge of the delegations the final report of the 51st JECFA Meeting, which would include the supporting toxicological monographs, is not yet available. This fact alone should prevent consideration of the proposed MRLs at this time.

	ADI	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)					
				Muscle	Fat	Liver	Kidney	Milk	Eggs
EU	0.5 µg/kg bw	Porcine	Doramectin	20	100	50	30	N/A	N/A
JECFA	0-0.5 µg/kg bw	Porcine	Doramectin	5	150	100	30	N/A	N/A

The EU-MRLs reflect the tissue distribution of residues in porcine and ovine species, which was slightly different from the pattern of distribution in cattle.

JECFA established the same MRLs for pigs as were previously adopted for cattle, with the exception of the value for muscle, which is 10 µg/kg for cattle and 5 µg/kg for pigs. However, the values established by JECFA would be compatible with the ADI to which the EU evaluations refer. Consequently, the differences do not lead to very different total intake of residues.

POSITION: The delegations do **not** support the JECFA/Codex MRLs if the supporting toxicological monographs are not made available.

Neomycin

	ADI	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)					
				Muscle	Fat	Liver	Kidney	Milk	Eggs
EU	30 µg/kg bw*	Bovine#	Neomycin	500*	500*	500*	5000*	500*	500*#
JECFA	0-60 µg/kg bw	Bovine✧	Neomycin	500	500	**15000✞**	**20000✞**	500	N/A

* Provisional ADI and MRLs
\# EU-MRLs also apply to ovine, caprine and porcine species and to chicken, turkey and duck
✧ JECFA also has established MRLs for sheep, goats, pigs, chicken, turkey, duck.
✞ Revision of existing values (500 µg/kg in liver, 10000 µg/kg in kidney).

The EU MRLs are provisional and will expire on 1 June 2000. They will be reconsidered. When the substance was evaluated for the EU, a higher safety factor was used due to insufficient data on genotoxicity. In the absence of additional data the delegations are not in a position to agree MRL-values as high as those proposed by JECFA.

POSITION: The delegations do **not** support the JECFA/Codex MRLs.

Phoxim

	ADI	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)					
				Muscle	Fat	Liver	Kidney	Milk	Eggs
EU	3.75 µg/kg bw	Porcine	Phoxim	*20**	*700**	*20**	*20**	N/A	N/A
JECFA	0-4 µg/kg bw	Bovine	Phoxim	50✞	400✞	50✞	50✞	10✞	N/A
		Porcine	"	50✞	400✞	50✞	50✞	N/A	N/A
		Ovine	"	50✞	400✞	50✞	50✞	none	N/A
		Caprine	"	50✞	400✞	50✞	50✞	none	N/A

* Provisional MRLs until 1 January 2001, not yet published
✞ Temporary MRLs until 2002

The data available for the EU evaluation were only sufficient to establish MRLs in pigs. The values follow the residue distribution in pigs. Data on residue depletion and routine analytical methods were insufficient for cattle, sheep and goats. The assessments of phoxim by the CVMP and JECFA were performed in parallel. Consequently, neither Committee was in a position to consider the other's decision.

POSITION: The delegations do **not** support the JECFA/Codex MRLs.

Porcine Somatotropin

The establishment of MRLs for porcine somatotropin was not requested in the EU and no information is available on the substances and no scientific evaluation has been initiated. Consequently, from our point of view, any decision on PST at this moment would be premature. This substance is similar to bovine somatotropin (BST). On BST the CODEX ALIMENTARIUS COMMISSION decided in its twenty-third session in ROME, 28 JUNE-3 JULY 1999 to hold the Maximum Residue Limits for Bovine Somatotropins at Step 8.

POSITION: The delegations do **not** support the JECFA/Codex MRLs.

Thiamphenicol

	ADI	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)					
				Muscle	Fat	Liver	Kidney	Milk	Eggs
EU	2.5 µg/kg bw	Bovine	Thiamphenicol	50	50	50	50	50	N/A
		Chicken	"	50	50	50	50	N/A	none
		Porcine*	"	50*	50*	50*	50*	N/A	N/A
		Ovine*	"	50*	50*	50*	50*	none	N/A
		Fish*	"	50*	N/A	N/A	N/A	N/A	N/A
JECFA	0-5 µg/kg bw✞	Porcine	Sum of thiamphenicol and thiamphenicol conjugates, measured as thiamphenicol✧	50*	50*	100*	500*	N/A	N/A

* Provisional MRLs: EU until 1 January 2001, JECFA until 2002
✧ The 52nd JECFA changed the definition of the marker residue, which previously was 'thiamphenicol'.
✞ The ADI was modified by the 52nd JECFA from 0-6 µg/kg bw to 0-5 µg/kg bw.
❖ The 52nd JECFA modified the MRL for fish at step 7 from 40 µg/kg to 50 µg/kg.
\# The 52nd JECFA withdrew the MRLs at step 7 for cattle and chicken tissues, as the required data had not been provided.

The ADI set by the EU evaluation is based on a microbiological endpoint. It is lower than possible toxicological ADIs and was considered more relevant. Consumer intake of residues based on EU-MRLs amounts to around 67% of the EU-ADI. It is not clear from the documents available to the EU, on which basis the ADI was established by JECFA.

POSITION: The delegations do **not** to support the JECFA/Codex MRLs.

Hormones: Progesterone, Testosterone, Estradiol-17 beta

Hormones: Progesterone, Testosterone, and Estradiol-17beta

To the knowledge of the delegations, the final report of the 51st JECFA Meeting, which would include the supporting toxicological monographs, is not yet available. This fact alone should prevent consideration of the proposed MRLs at this time.

In any case, the natural hormones Progesterone, Testosterone and Estradiol-17beta may be used for therapeutic purposes and as growth promoters. If these hormones are used for growth promotion, they will be used during a prolonged period of time and, therefore, would increase the level of residues in the body of the animal. Conversely, the use for therapeutic purposes is usually occasional and an obligatory withdrawal period before slaughter will avoid residues in edible tissues. The JECFA evaluation does not make a clear distinction between these two uses.

The independent Scientific Committee on Veterinary Measures Relating to Public Health (SCVMPH) of the European Union has published a report on the assessment of potential risks to human health from residues of six hormones, including the above three natural hormones, in bovine meat and meat products, which focuses on the use of hormones as growth promoters. Its major conclusions are:

– As concerns excess intake of hormone residues and their metabolites, and in view of the intrinsic properties of hormones and epidemiological findings, a risk to the consumer has been identified, with different levels of conclusive evidence for the 6 hormones in question.

– In the case of 17 beta oestradiol there is a substantial body of recent evidence suggesting that it has to be considered as a complete carcinogen, as it exerts both tumour initiating and tumour promoting effects. The data available does not allow a quantitative estimate of the risk.

– For the other 5 hormones, in spite of the individual toxicological and epidemiological data described in the report, the current state of knowledge does not allow a quantitative estimate of the risk.

– For all six hormones, endocrine, developmental, immunological, neurobiological, immunotoxic, genotoxic and carcinogenic effects could be envisaged. Of the various susceptible risk groups, prepubertal children is the group of greatest concern. Again the available data do not enable a quantitative estimate of the risk.

– In view of the intrinsic properties of the hormones and in consideration of epidemiological findings, no threshold levels can be defined for any of the 6 substances.

Unlike products used for occasional therapeutic or zootechnical purposes under veterinary supervision, the widespread use of growth promoters may lead to systematic and long-term exposure of consumers to harmful residues. The additional risk resulting from the use of these hormones as growth promoters, together with problems associated with lack of control or potential for misuse, must also be taken into account. Any Member of Codex is free to decide its level of health protection in its territory, which implies that they may decide to accept as a "natural or inevitable risk" the risk arising from the naturaly occuring hormones in humans and animals, but may decideto reject any additional risk resulting from exogenously administered hormones which mimic the biological and chemical action of the natural hormones.

POSITION: The delegations do **not** support the JECFA/Codex MRLs.

Consumers International

General Comments

Consumers International notes that only the summary and conclusions of the JECFA meeting are currently available, not the full report of the meeting. We recognize that this is common practice, to request comments from national governments and interested international organizations on the conclusions of JECFA without having a full report available. We also recognize that there are resource and other difficulties in producing reports in a more timely manner. We further recognize that additional detail regarding the assessment of some of the more controversial compounds was provided in an annex to the summary report. At the same time, it must be acknowledged that this practice makes it very difficult for Codex to resolve differences and achieve consensus on controversial issues.

In particular, the science relevant to issues regarding hormones has been undergoing significant review lately, and there is not a scientific consensus. Different scientific bodies have reached different conclusions on the issue. Shortly after the 52nd JECFA, an Opinion was issued by the Scientific Committee on Veterinary Measures Related to Public Health (SCVMPH), to the European Commission. This Opinion is a lengthy scientific document and is available at http://europa.eu.int/comm/dg24/health/sc/scv/out21_en.pdf. The SCVMPH has concluded, in contrast to JECFA, that no threshold level and therefore no ADI can be established.

Consumers recognize that there are on-going debates about the safety for consumers of hormones used in beef production, with different views being taken by countries, scientists, and scientific bodies. Similarly, there have been differences in how consumers worldwide perceive the safety of hormone-treated beef, as well as environmental, and ethical issues regarding the use of hormones in beef production .

Recently, a consensus statement (attached) on the subject of beef hormones was prepared by the Transatlantic Consumer Dialogue (TACD). The Transatlantic Consumer Dialogue is a forum of US and EU consumer organizations which develops and agrees joint consumer policy recommendations to the US government and European Union (EU) to promote the consumer interest in EU and US policy making. It aims to provide a formal mechanism for EU and US consumer representatives to input to EU and US political negotiations and agreements as well as explore ways of strengthening the EU and US consumer view at the international level. Over 60 consumer organizations in Europe and the US participate in the TACD. More information on the TACD is available at http://www.tacd.org/.

Consumers International agrees with the TACD that there should be recognition that the current state of scientific knowledge and the existing scientific uncertainties provide a reasonable basis for differing scientific conclusions and differing national decisions, including both the EU's precautionary approach and the US's permissive approach. We hope that the JECFA report, once it is made available, may help to shed some light on the current state of scientific knowledge and help to resolve some of the scientific debates.

Comments on JECFA Conclusions on Estradiol-17Beta, Progesterone, and Testosterone

JECFA has established ADIs for the 3 hormones (0-0.05 ug/kg bw for estradiol-17Beta, 0-30 for progesterone, and 0-2 for testosterone), and MRLs of "not specified." An MRL "not specified" means that

> "available data on the identity and concentration of residues of the veterinary drug in animal tissues indicate a wide margin of safety for the consumption of residues in food when the drug is used according to good practice in the use of veterinary drugs. For that reason, and for the reasons stated in the individual evaluation, the Committee concluded that the presence of drug residues in the named animal product does not represent a health concern and that there is no need to specify a numerical MRL."

For estadiol-17 Beta, JECFA's ADI is based on a NOEL for changes in several hormone-dependent parameters in post-menopausal women, divided by a 100-fold safety factor (10 for normal inter-individual variation and an additional factor of 10 "to protect populations of various sensitivities"). Similarly, for progesterone, JECFA established an ADI based on a LOEL for changes in the uterus in adult women, divided by a 100-fold safety factor (10 for normal inter-individual variation and 10 to allow for extrapolation from a LOEL to a NOEL). For testosterone, JECFA based its ADI on a NOEL for sexual function indices in (five) eunuchs, divided by a 1000-fold safety factor ("to protect populations of various sensitivities", and because of the small number of subjects in the study used to identify the NOEL).

Consumers International is concerned that the JECFA toxicological assessments for these three compounds may not be sufficiently sensitive, since they focus on adults

and on lifetime exposure, rather than exposure during critical windows of vulnerability during development. For example, research by Frederick vom Saal at the University of Missouri indicates just how exquisitely sensitive the developing fetus is to endogenous hormones. The effects on a rodent pup from even the minuscule amount of hormones resulting from being surrounded by brothers in the womb compared to being surrounded by sisters are measurable and significant.

Furthermore, although there may be a threshold level for the effect of hormones on some endpoints, such as estrogen on serum levels of corticosteroid-binding globulin (CBG), we do not know how such a threshold level relates to other effects of hormones, particularly during exposure during critical periods of development. For example, we are not convinced that an ADI based on a NOEL for changes in CBG adequately addresses the cancer risks posed by estrogen. And as the JECFA assessment described in the Annex notes, epidemiological studies on women who took estrogen show that the risks for cancer of the endometrium and of the breast are increased. While there are a number of endpoints that are hormonal in nature, that does not imply that the NOEL for one endpoint (e.g., changes in serum CBG) will also be a NOEL for other hormonally-related endpoints (e.g., pre-cancerous changes leading to breast or endometrial cancer, or developmental effects).

We are also concerned and do not see a rationale in the summary annex as to why JECFA did not use an additional factor "to protect populations of various sensitivities" for progesterone.

Regarding the residue data, we question whether the median value of a residue is the appropriate value to be used, given the concern for short-term exposures during critical periods of development. Occasional high "spikes" might be a greater concern, and perhaps the 95th or 97.5th percentile residue level would be the more appropriate criterion for estimating risks, rather than the median.

Overall, we remain troubled by the lack of scientific consensus on these issues and are not confident that JECFA's as yet unpublished report provides a valid scientific rationale for the recommended "MRL's not specified." We believe the central question of what limits would sufficiently protect consumers from possible effects of low-level exposures to potent hormonal substances, especially during developmentally sensitive periods, has not been adequately answered, as reflected in the divergence of conclusions between the JECFA and SCVMPH reports. We therefore urge CCRVDF not to progress this issue toward a decision unless and until there has been an opportunity to resolve some of the important open scientific issues.