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 6 (b) **CX/RVDF 04/15/4A**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS
Fifteenth Session
Washington, DC (metro area), (United States of America), 26- 29 October 2004

DRAFT AND PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS

Comments submitted by Argentina, Canada, Egypt, United States and IFAH in response to CL 2004/17-RVDF

GENERAL COMMENTS

ARGENTINA

The tasks and duties in risk analysis and its applications in the area of Public Health should be clearly taken up by each of the decision makers. For the purposes of transparency, it is of great importance that risk assessment should be clearly separated from risk management, as established in the general principles of Codex Alimentarius and WORKING PRINCIPLES FOR RISK ANALYSIS FOR APPLICATION IN THE FRAMEWORK OF THE CODEX ALIMENTARIUS (Alinorm 03/41, Appendix IV), which are referred to and stressed in the Summary and Conclusions of the 62nd Meeting of the JOINT FAO/WHO EXPERT COMMITTEE (JECFA). This independence helps ensure the objective assessment of the impact that the incorporation of residues of a veterinary drug in the food chain might have. It also provides risk managers with science-based information when making decisions.

It should be borne in mind that this information should be not only well grounded, but also clear; it should be easily available in a timely manner, so that those who must take up risk-management responsibilities do not lack information.

A clear example is the change concerning flumequine between the 60th and the 62nd JECFA meeting. In this particular case, the acceptable daily intake and the maximum residue limits in connection with this drug were removed at the 60th meeting and re-established at the 62nd meeting.

Without going into the reasons for this change—which are unquestionable—there is confusion within risk management which creates, to a great extent, difficulties in the decision-making process and calls into question the overall procedure.

Specific Comments

In order to reduce the level of confusion, it is a key rule in any communication process to increase the amount of information available. The availability of information is very important for decisions taken by risk managers to be based on real knowledge of the state of affairs in assessment and to avoid the potential adverse effects of hasty decisions.

Ideally, the grounds for each JECFA recommendation would be published together with the summary and conclusions of each meeting. As we know, this would imply a lot of work for JECFA, as it would require great administrative support, which would increase the costs of meetings.

A half-way situation would be to include, in the summary and conclusions of each meeting, the grounds of the most important decisions, as is the case with the removal and re-establishment of ADI and MRL for flumequine.

Regardless of this, access to full reports is very limited for two reasons. To begin with, paper publication takes quite long, and distribution is scarce. As a result of this delay, publications are not available before the meeting at which the Codex Committee on Residues of Veterinary Drugs in Foods is to discuss the issues.

Access through the web page is limited as well, mainly because the reports are not on the page. Previous reports can be easily accessed through other pages that have published them, ordered according to the active pharmacological substance, but this does not extend to reports presently under discussion.

The electronic publication of full reports in a timely manner in order to enable the correct assessment by risk managers on a web site designed to facilitate the find of information would help to increase participation, facilitating the decision-making process by means of a transparent mechanism, so as to prevent the appearance of health problems or the development of unjustified barriers to trade.

CANADA

60th JECFA Meeting

Canada has noted the recommendations on maximum residue limits for veterinary drugs (MRLVDs) arising from the 60th JECFA meeting and supports JECFA's recommendation for the withdrawal of MRLs for Carbadox.

62nd Meeting

Canada has noted the recommendations on maximum residue limits for veterinary drugs (MRLVDs) arising from the 62nd JECFA meeting and reserves comment on the MRLVD recommendations until a full JECFA report is available for review.

EGYPT

Recommendations are accepted including:

- Neomycin at step 6
- Imidocarb at step 3
- Dicyclanil at step 6
- Trichlorfon
- Carbadox withdrawn
- Cefuroxime at step 5
- Flumequine at step 6
- Lincomycin
- Pirlimycin at step 3
- Cygalothrin at step 6
- Cypermetrhrin and alpha-cypermetrin at step 3
- Doramectin at step 3
- Phoxim at step 6
- Melengestrol acetate at step 6
- Ractopamine at step 3

SPECIFIC COMMENTS

Neomycin

No comment submitted.

Imidocarb

UNITED STATES

The United States supports adoption of the draft standard in cattle tissues and milk.

Dicyclanil

IFAH

Introduction

An addendum to the dicyclanil monograph (prepared by the 54th meeting of the Committee and published in FAO Food and Nutrition Paper 41/13, 2000) was published in the FAO FNP 41/15, 2003. The MRLs were set as shown in Table 1 below.

IFAH would like to draw attention to some problems it sees with the approach taken by the JECFA 2003. The main issue arises from the fact that the parent molecule dicyclanil is defined as the sole marker residue.

Marker residue

The conclusions are not consistent with those of the European Union, New Zealand or Australia, in that JECFA defines the marker residue as dicyclanil alone, while in all the other territories it is the sum of dicyclanil and the metabolite CGA 297107. In the Summary report of the 60th meeting JECFA reiterated that choice of a single marker residue is preferred. On page 5 under the heading "Considerations on marker residues", the last sentence provides additional flexibility to the concept of selecting a single marker compound, whenever possible. IFAH feels that for dicyclanil, it would be possible, practical, scientifically justified, and consistent with other national and international bodies, to include the parent and the metabolite CGA 297107 in the marker residue definition.

Ratio of marker residue to total residue

The JECFA evaluation concludes that 28 to 32 days post dose, the only residues of concern are dicyclanil and CGA 297107. Since no radiolabel data are available for this time point, this is difficult to justify. No explicit guidance on the ratio of marker to the total residues is provided in the evaluation. It has to be assumed that this ratio can directly be derived from the MRL and the "concentrations of total residue of concern", expressed as dicyclanil. Taking this approach, the ratios of marker to total residues would be 0.3676 for liver and kidney, 0.6522 for muscle, and 1 for fat.

Thus the results of the calculations of daily intakes of total toxicologically relevant residues, and their comparison to the ADI are quite different from those established in the EU (see Tables 1 and 2). There is no rational why this should be so.

The authors conclude in the appraisal that a TMDI can not be calculated for residues occurring before 28 days. This would mean that any consumption of food exceeding the MRL can not be assessed as to its toxicological relevance. The situation when the dose was exceeded will be entirely different from that when the waiting period was not observed. It will be difficult or even impossible to interpret and toxicologically appraise any violations of the MRL.

Table 1: JECFA 2003, Dicyclanil MRLs in Sheep, (ADI = 0.42mg/Person)

Food commodity	MRL (µg/kg)	(% Total)	Concentration of total residue of concern[1)] (µg/kg)	Consumption (g/person/day)	Total intake µg/person
Liver	125	(36.76)	340	100	34.00
Kidney	125	(36.76)	340	50	17.00
Muscle	150	(65.22)	230	300	69.00
Fat	200	(100)	200	50	10.00
TMDI					*130.00*
% ADI					*31*

1) The upper limit of the 95% confidence interval for the 95th percentile of the sum of the concentrations of dicyclanil and the metabolite CGA 297107, expressed as equivalents of dicyclanil

Table 2: EU 2000, Dicyclanil plus CGA 297107 MRLs in Sheep, (ADI = 0.42mg/Person)

Food commodity	*MRL (µg/kg)*	% Total	Concentration of total residue of concern (µg/kg)	Consumption (g/person/day)	Total intake µg/person
Liver	*400*	15	2670	100	267
Kidney	*400*	25	1600	50	80
Muscle	*200*	100	200	300	60
Fat	*150*	100	150	50	7.5
TMDI					*414.5*
% ADI					*≈98.5*

Withdrawal period (WDP)

Currently, the following specifications exist in countries where CLIK is marketed:

EU WDP = 40 days for all sheep, do not shear for 3 months after treatment

Australia WDP = 28 days for all sheep

New Zealand WDP = 35 days (other than Merino breed), 56 days (Merinos)

With the proposed JECFA MRLs, yet different withdrawal periods could be calculated.

Conclusion

The current JECFA evaluation does not seem to appreciate the current efforts to harmonize the assessments of residues from veterinary medicines. It is not transparent in that it does not provide detailed methods and calculations for the appraisal. Thus it is not possible to retrace how the conclusions were reached.

For the sake of harmonization, transparency and consistency, IFAH proposes to

1. reconsider again the selection of dicyclanil alone as the marker residue
2. publish the detailed methodology for calculating the current MRLs
3. specify explicitly the ratio of total residue to marker residue

Trichlorfon (Metrifonate)

No comment submitted.

Carbadox

CANADA

Canada has noted the recommendations on maximum residue limits for veterinary drugs (MRLVDs) arising from the 60th JECFA meeting and supports JECFA's recommendation for the withdrawal of MRLs for Carbadox.

UNITED STATES

The United States recommends any action be deferred on the 60th JECFA recommendation to withdraw the MRLs for carbadox. The U.S. agrees with JECFA that "… there is no evidence that any harmful effects have been caused by residues of this compound that may have been present in food resulting from approved uses in animals." In addition, the U.S. Delegation is concerned that the withdrawal of the existing MRLs will have an adverse impact on trade and animal health. The U.S Delegation recommends that the MRLs remain in place until several current activities within FAO, WHO and Codex Committees are completed and any resulting recommendations regarding safety assessments of carcinogenic compounds are evaluated and adopted by the CCRVDF:

a. The adoption by CCRVDF of a Risk Assessment Policy for evaluating carcinogenic compounds by JECFA.

b. The completion of FAO/WHO Project Update.

c. The Joint FAO/WHO Technical Workshop on Residues of Veterinary DrugsWithout ADI/MRLs recently held in Bangkok.

d. FAO/WHO Workshop on Dose Response scheduled for September 2004 in Geneva.

BACKGROUND:

- MRLs for a persistent metabolite of carbadox (QCA) in swine liver and muscle were recommended by the 36th JECFA and adopted by the 20th session of the Codex Alimentarius Commission (1993). The MRL permitted the use of carbadox in pigs only when an extended withdrawal time was observed.
- The parent drug carbadox and another metabolite, desoxycarbadox, were determined to be carcinogenic. However, both carbadox and desoxycarbadox were undetectable within a few days after withdrawing the feed containing carbadox. Based on new data from residue studies in pigs that were not adequately withdrawn from feed containing carbadox, Canada requested a new evaluation by JECFA.
- The sponsor submitted new residue data using a new analytical method which detected carbadox and desoxycarbadox at withdrawal times up to about 15 days but still much less than the FDA withdrawal time required for QCA to deplete below the established MRL. Based on this data and a fundamentally different risk assessment policy to evaluate animals drugs, JECFA withdrew the MRL for carbadox. That policy was based on an IPCS guideline that stated that an ADI could not be established for carcinogens.[1]
- At the same time JECFA stated that "…Notwithstanding this decision [to no longer support MRLs], consumers should have every confidence that there is no evidence that any harmful effects have been caused by residues of [this compound] that may have been present in food resulting from approved uses in animals."
- Carbadox is a good example of the need for quantitative risk assessment policy in JECFA and Codex. As analytical methods detection levels in the parts per billion (µg/kg) and parts per trillion (ng/kg) become more and more common, a risk assessment policy that is both protective of public health and cognizant of the fact that many constituents of food are carcinogenic to animals when fed at high doses. Examples include food additive constituents, contaminants, impurities, metabolites, flavors and flavor extracts and food contact materials.
- In the USA, because of a special exemption in the law "carcinogenic" animal drugs can be approved as safe for human food if the carcinogenic substance can not be detected under labeled conditions of use (i.e., if a risk assessment determines that there will be no or only *de minimis* exposure to the carcinogen).

- The above three FAO/WHO projects all are exploring the concept of developing contemporary risk assessment policies. The FAO/WHO Workshop on Dose Response in Geneva, 13-17 September 2004, will explore whether thresholds of carcinogenic compounds can be established. This project is critical to replacing standards set by the available analytical methods with information obtained from the toxicological properties of a compound. The Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs Without ADI/MRLs has discussed, among other things, whether *de minimis* levels can be established. Project Update is an update of the risk assessment policy in the current Environmental Health Criteria 70: *Principles for the Safety Assessment of Food Additives in Food.* This publication is the basis of the current policies used by JECFA (published prior to any JECFA meting for veterinary drugs).
- The 26th Session of Codex Alimentarius Commission adopted the "*Working Principles For Risk Analysis For Application In The Framework Of The Codex Alimentarius*". These principles state that CCRVDF is responsible for the risk assessment policy for veterinary drugs. Regardless of the outcome of the above three projects CCRVDF is responsible to adopt some policy guidance for JECFA on how JECFA should evaluate the safety of carbadox (and other veterinary drugs) and recommend to the Commission whether the carbadox MRLs should be retained or withdrawn.

[1]Sonich-Mullin, C. et al., IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis, Reg. Toxicol. Pharmacol., 34, 146-152.

Cefuroxime

No comment submitted.

Flumequine

UNITED STATES

(MRLs for Flumequine in cattle, chickens, pigs and sheep at Step 6)

The United States supports the re-establishment of an ADI and the recommended MRLs. The U.S. has reviewed the evaluation report submitted by JECFA and in the interest of animal and human food safety is in agreement with their conclusions.

BACKGROUND:

- The Acceptable Daily Intake (ADI) was re-established at the 62nd JECFA based on new data indicating an absence of genotoxic potential.
- The MRLs are full MRLs in all edible tissues in cattle, chickens, pigs and sheep. The MRL established for shrimp is temporary. The MRL for trout is muscle with the skin in normal proportions.
- The MRLs are those recommended at the 54th JECFA

Lincomycin

UNITED STATES

The U.S. supports the JECFA conclusion to not recommend MRLs for lincomycin in cattle tissue. The U.S. can support the draft standards for tissues of pigs and chickens.

Pirlimycin

UNITED STATES

The U.S. Delegation supports the tissue MRLs for pirlimycin, but does not support the MRL recommended for milk. The MRL for milk recommended by the 62nd JECFA was elaborated at 100 µg/kg. Significant differences remain with respect to global assessment procedures that could negatively impact international trade. The MRL for milk is inconsistent with the U.S. tolerance of 400 µg/kg and could impart unnecessary discard of milk.

The U.S. notes that JECFA considered effects on starter cultures from residues in milk in recommending a MRL in milk. The terms of reference for JECFA noted in the 62 report indicated "…recommending MRLs for such residues …in food-producing animals in accordance with good practice in the use of veterinary drugs, and to evaluate the safety of residues of certain veterinary drugs". The terms of reference do not indicate consideration of food processing in recommending MRLs. We consider this latter point to be a risk management decision for national authorities.

Cyhalothrin

No comment submitted.

Cypermethrin and Alpha-cypermethrin

UNITED STATES

The United States supports advancing the recommended MRLs because the ADI and MRLs are harmonized and permanent.

Doramectin

UNITED STATES

For international trade purposes, the U.S. Delegation can support the MRL of 15 µg/kg for doramectin in cattle milk, but questions the purpose and accuracy of the footnote included as part of the assessment. Conclusions with respect to good veterinary practice or potential withdrawal times are not part of the JECFA terms of reference as these represent risk management issues within the purview of CCRVDF and/or its individual Member Countries. The footnote, with respect to doramectin, does not apply globally as the methodology for calculating a withdrawal time varies considerably across regions. The U.S. Delegation is of the opinion that the footnote raises unnecessary concerns for food safety and for international trade and should be deleted.

Phoxim

No comment submitted.

Melengestrol Acetate

UNITED STATES

This responds to CL 2004/17-RVDF which requests comments on Maximum Residue Limits for Veterinary Drugs (MRLVDs) arising from the 60th and 62nd Meeting of JECFA. The United States appreciates the opportunity to provide the following comments for consideration at the forthcoming 15th Session of the Codex Committee on Residues of Veterinary Drugs in Foods.

Melengestrol Acetate in cattle tissues at the 15th CCRVDF at Step 6.

The U.S. Delegation supports JECFA's scientific review and assessment of the new metabolite data for MGA. The U.S. Delegation is of the opinion that these data are critical to the accurate evaluation of this compound with respect to establishment of appropriate MRLs.

However, the U.S. Delegation does not support the recommended MRLs because the U.S. has become aware of an inconsistency in the approach used to derive the recommended MRLs. The U.S. Delegation cannot support the proposed MRLs without correction of this inconsistency. This resulted from the initial elaboration of the ADI on progestagenic activity and the subsequent recommended MRLs on the basis of total residues. Significant differences still remain between the U.S. tolerance for MGA and the proposed MRLs (as written) and will continue to negatively impact international trade. The U.S. Delegation proposes that the final report of the 62nd JECFA contain a corrective note to indicate that the MRLs were calculated on a different basis than the ADI.

BACKGROUND:

- The 54th JECFA recommended MRLs for fat (5 µg/kg) and liver (2 µg/kg). As inadequate information was available on structure and activity, the metabolites were assumed to be as progestagenic as the parent drug. As such, a marker to total residue correction was (appropriately) applied to account for this potential additional activity. The Committee utilized 50% of the available ADI.
- New data on the relative activity of the MGA metabolites were submitted to the 62nd JECFA. The Sponsor concluded that the progestogenic activity of the metabolites was substantially less than MGA parent. The 62nd JECFA agreed with this assessment following review of the dossier and assigned a conservative value of 12% relative activity to the MGA metabolites.
- The 62nd JECFA recommended an increase in the MRLs for MGA to 8 µg/kg for fat and 5 µg/kg for liver, which utilized 93% of the ADI in the approach used by JECFA. However, if the total residue correction had not been applied, MRLs of 16 µg/kg for fat and 10 µg/kg for liver could have been elaborated, utilizing 100% of the ADI.
- In its calculation of the MRLs, the 62nd JECFA appropriately discounted the activity of the MGA metabolites, but continued to apply a marker to total ratio correction factor to the residues, thus effectively adding back the majority of the activity for the metabolites that it had just discounted. Since the ADI is based on progestagenic activity and the residues had now been evaluated on the same basis of remaining activity (of MGA and its metabolites), this total residue correction is no longer necessary.

Table 1: Activity Weighting

Tissue	% of total radioactive residue attributable to:		% of progestogenic activity attributable to:		
	MGA[(a)]	Non-MGA residues	MGA	Non-MGA residues[(b)]	Sum of MGA and non-MGA residues
Fat	85	15	85 x 1	15 x 0.12 = 1.8	85 + 1.8 = 87
Liver	33	67	33 x 1	67 x 0.12 = 8.04	33 + 8.04 = 41

(a) Data from 58th JECFA

(b) Relative potency of Metabolite E (12%) applied to all non-MGA metabolites

Table 2: Maximum Daily Intake Calculations

Tissue	MRL (µg/kg)	Marker residue / total residue (c)	Total residue (µg/kg)	Diet (kg)	Intake of residues (µg/kg)
	JECFA MRLS				
Fat	8	0.87	9.2	0.05	0.46
Liver	5	0.41	12.2	0.1	1.22
				Total	1.68
				% ADI (1.8 µg):	**93**
	POSSIBLE MRLs				
Fat	16	1	16.0	0.05	0.80
Liver	10	1	10.0	0.1	1.00
				Total	1.80
				% ADI (1.8 µg):	**100**

MR/TR ratio is based on % progestogenic MGA activity
(c) equivalents from previous table

Ractopamine

UNITED STATES

Draft standard for MRLs in cattle and pig tissues for Ractopamine

The U.S. Delegation supports the advancement of MRLs for ractopamine hydrochloride. The MRLs provide a reference point for governments as they differentiate ractopamine hydrochloride from others in the class and as they seek to ensure the safe use of beta agonist products within their country.

The U.S. delegation notes that extensive toxicology studies were considered by the U.S. FDA including long term chronic toxicity and multiple studies on genotoxicity and carcinogenicity in determining the ADI for ractopamine. FDA determined that the most relevant study was a one-year chronic toxicity study in monkeys. The U.S. delegation also notes that the toxicological considerations raised by JECFA in 1993 were adequately addressed in the 1999 U.S. FDA approval.

The understanding of JECFA's toxicological procedures for establishing a full ADI indicate that the 62nd JECFA considered that all the toxicology concerns noted by the JECFA in its 1993 report had been adequately addressed by relevant studies.

The U.S. Delegation is concerned that the recommended MRLs are significantly lower than the U.S. tolerances, and those established by most other countries. Part of this difference can be attributed to the effect of rounding the ADI to one significant figure. JECFA is urged to revise the MRLs to eliminate the effect of rounding the ADI. However, as the MRLs are only at Step 3, the U.S. supports advancing the MRLs for ractopamine hydrochloride to Step 5. The U.S. reserves its right to modify its position pending the decisions at the 15th Session of CCRVDF.

BACKGROUND:

- The U.S. ADI differs (0-1.25 µg/kg per day versus 0-1 µg/kg per day) from the JECFA established ADI because JECFA rounded the calculated ADI to one significant figure, thereby reducing the theoretical maximum daily intake attributed to recommended MRLs by 25%.
- Tolerances in the U.S. are calculated on a different basis than JECFA recommended MRLs, contributing to significantly lower MRLs than U.S. tolerances (U.S. tolerance in pig muscle and liver are 50 and 150 µg/kg, respectively: JECFA MRLs in muscle and liver are 10 and 40 µg/kg, respectively).

- Historically in Codex, production aid products have been controversial. Efforts to arrive at more accommodating MRLs should not compromise efforts to achieve an international standard.