

EUROPEAN COMMUNITY COMMENTS ON

CL 2004/17-RVDF

Subject: REQUEST FOR COMMENTS:

- A) Recommendations on maximum residue limits from the 60th and 62nd meetings of JECFA**
- B) Priority list of veterinary drugs for evaluation or re-evaluation**

- A)** The European Community would like to present the following comments to the recommendation on maximum residue limits for veterinary drugs arising from the 60th and 62nd meetings of the Joint FAO/WHO Expert Committee on food additives. It should be pointed out that the detailed reports from the 62nd meeting were not available for a final opinion regarding the substances considered at that meeting.

These comments relate to positions for draft MRLs for the following substances:
Neomycin for bovine tissues and milk (at step 6),
Imidocarb for bovine tissues and milk (at step 3),
Dicyclanil for ovine tissues (at step 6),
Trichlorfon/metrofonate (step 6)
Carbadox for porcine tissues (withdrawn),
Cerfuroxime for bovine milk (step 5 – withdrawn)
Flumequine for bovine, ovine, porcine, chicken, trout and shrimp tissues (at step 6 and 3)
Lincomycin for cattle tissues (no proposal from JECFA)
Pirlimycin for bovine tissues and milk (step 3)
Cypermethrin and alphacypermethrin for bovine and ovine tissues and bovine milk (at step 3)
Doramectin for bovine milk (at step 3)
Phoxim for caprine tissues (at step 6)
Melengestrol acetate for bovine tissues (at step 6)
Ractopamine for bovine and porcine tissues (at step 3)

Cyhalothrin for bovine, ovine and porcine tissues and bovine milk provided that a validated analytical method is available.

The maximum residue limits proposed for **neomycin, imidocarb, dicyclanil, flumequine, pirlimycin, cyhalothrin, cypermethrin, alphacypermethrin** and **phoxim** provide for appropriate protection of consumer safety and are therefore acceptable.

The proposals to withdraw the previous draft maximum residue limits for **carbadox** and **cefuroxime** are supported. Likewise, there was no proposal for new maximum residue limits from JECFA for **lincomycin** and the conclusions are supported.

The proposed maximum residue limits for the following substances can not be supported due reasons provided for each substance:

- **Trichlorfon/Metrifonate:** The European Community cannot accept the adoption of maximum residue limits for this substance, due to clear evidence of mutagenicity both *in vitro* and *in vivo*. Furthermore, there is evidence, which JECFA has accepted, that it is a germ cell aneugen *in vivo*. There is no evidence of a NOEL for these effects and no new information suggesting that these data are not valid. There are a number of other reasons against the proposed Acceptable Daily Intake (ADI) and marker residue for trichlorfon/metrofonate:
 - The derivation of a No (Low) Effect Level (N(L)OEL) of 0.2 mg trichlorfon/kg bodyweight in human patients from a small increase of acetylcholine esterase inhibition after the reduction of the dose from 0.5 mg/kg to 0.2 mg/kg is not based on sound scientific considerations. It is inappropriate to base an ADI on a LOEL from clinical trial data involving a diseased sub-set of an aged sub-group of the human population.
 - There is no clear overall NOEL for developmental toxicity due to effects on brain hypoplasia in pigs. There is evidence that such effects may be due to effects on DNA that are unclear and for which no NOEL is evident.
 - There is evidence of delayed neurotoxicity, albeit at high doses in humans and primates. Such effects are generally regarded as non-threshold effects.
 - The major active metabolite of trichlorfon is dichlorvos. No ADI for this substance has been proposed.
 - The marker residue identified by JECFA was the parent substance. Assessment of data on the pharmacokinetics of trichlorfon suggests that the parent substance has a short half-life of only 1 to 2 hours, indicating that it would be unsuitable as a marker residue.
- **Doramectin:** The proposed ADI and maximum residue limits for bovine milk could in principle be acceptable. The European Community, however, shares the concerns raised by JECFA that the resulting long discard periods of 10 to 20 days may not be complied with in practice, leading to concerns about consumer safety. The proposal for establish maximum residue limits for bovine milk are therefore not supported.
- **Melengestrol acetate and ractopamine:** The substances were evaluated by JECFA for use as growth promoters. Such use of hormones with estrogenic, androgenic or gestagenic action and beta agonists are prohibited in the European Union.

Concerning melengestrol acetate, the concerns are that by excess intake of hormone residues and their metabolites, endocrine, developmental, immunological, neurobiological, immunotoxic, genotoxic and carcinogenic effects

could be envisaged, in particular for susceptible risk groups. The European Community can therefore not support the adoption of the proposal for maximum residue limits for this substance.

Ractopamine is a beta-agonist. It has been evaluated earlier by JECFA in 1993. In the publicly available report it was noted that:

- (a) some β -adrenoceptor agonists were carcinogenic;*
- (b) no long-term studies had been conducted in rodents; and*
- (c) there were no data relating to the long-term exposure of humans to ractopamine.*

JECFA therefore requested additional data to assess the safety of ractopamine in the areas of genotoxicity, pharmacology and long-term effects on human beings. In particular data was requested on in vivo genotoxicity, sufficient data to determine the most sensitive indicator for the establishment of a pharmacological NOEL and a survey of all non-therapeutic effects that follow long-term β -adrenoceptor agonist use in humans, to assist in the prediction of the consequences of the long-term intake of residues of ractopamine by consumers of animal meat. JECFA concluded *“that depending on the results of the above investigations, it may be necessary to perform other studies to explore further the potential carcinogenicity of ractopamine”*.

Given that the detailed report from the 62nd JECFA meeting is not yet available, it is impossible to verify whether these issues have been sufficiently addressed in the recent JECFA evaluation and therefore to form a final opinion on the safety of the substance. The European Community can therefore not support the proposal for maximum residue limits for this substance.

- B)** No specific comments can be offered on the priority list of veterinary drugs for evaluation or re-evaluation.