



**JOINT FAO/WHO FOOD STANDARDS PROGRAMME**  
**CODEX ALIMENTARIUS COMMISSION**  
**Forty-fourth Session**

**AMENDMENTS TO THE PROCEDURAL MANUAL**

**Proposal from the 25<sup>th</sup> Codex Committee on Residue of Veterinary Drugs in Foods (CCRVDF25)**

1. CCRVDF is proposing an approach for Extrapolation of Maximum Residue Limits of Veterinary Drugs to one or more species, as listed below to be included in the Procedural Manual (Section IV: Risk Analysis, Risk Analysis Principles Applied by the Codex Committee on Residue of Veterinary Drugs in Foods, Annex C“).
2. CCRVDF25 agreed “to forward the approach for extrapolation as revised to CAC44 (2021) for adoption and inclusion as Annex C to the Risk Analysis Principles Applied by CCRVDF.” CCRVDF25 also agreed to include a footnote in paragraph 30, 2<sup>nd</sup> bullet point as follows: “the approach for the extrapolation of MRLs for veterinary drugs to one or more species is presented in Annex C to these principles”.
3. The Commission is invited to adopt the amendments to the Procedural Manual as contained in Annex I.
4. Comments received are contained in CX/CAC 21/44/2 Add.3.

Codex Body	Text	Reference
CCRVDF	Amendment to the Procedural Manual, Risk Analysis principles applied by CCRVDF: Approach for the extrapolation of MRLs for veterinary drugs to one or more species	<ul style="list-style-type: none"> <li>• REP21/RVDF, paragraph 105(i,ii), Appendix III</li> <li>• Annex I of this document</li> </ul>

**AMENDMENTS TO THE PROCEDURAL MANUAL:  
RISK ANALYSIS PRINCIPLES APPLIED BY THE CODEX COMMITTEE ON RESIDUES OF  
VETERINARY DRUGS IN FOODS**

**Part A**

**ANNEX C: APPROACH FOR THE EXTRAPOLATION OF MAXIMUM RESIDUE LIMITS OF VETERINARY DRUGS TO ONE OR MORE SPECIES**

**General criteria for extrapolation:**

1. Extrapolation should take place only between the same tissues/food commodities in the reference and concerned species (e.g. muscle to muscle, fat to fat etc.).
2. Extrapolation of reference species MRLs to a concerned species on a one to one basis should be considered only if all of the following are satisfied:
  - (i) the reference and concerned species are related (see “A note on terminology” below),
  - (ii) the marker residue in the reference species is the parent compound only, or is the same as the total residues of toxicological concern, or the Codex MRL status in the reference species is ‘unnecessary’ and there is an expectation that the active substance will be used under the same conditions (i.e. by the same administration routes and at similar doses) in both species.
  - (iii) the M:T<sup>1</sup> (the marker ‘M’ to total residues of toxicological concern ‘T’) established for the reference species can be applied to the concerned species.

**Specific criteria for extrapolation**

3. In order to ensure that the third of the above-mentioned three general criteria is satisfied, the following specific criteria are proposed.
  - (i) Where identical Codex MRLs have been established in at least two related species on the basis of JECFA recommendations or there is good reason to consider extrapolation from just one related species, these Codex MRLs can be extrapolated to other related species (e.g. extrapolate from cattle and sheep to all ruminants).

***Explanatory note:** The existence of identical MRLs in two related species provides grounds upon which to base the assumption that metabolism does not vary significantly within the group of related species—i.e. that the M:T established for the reference species can be applied to the concerned species.*

- (ii) Where identical M:T values have been used in JECFA calculations for two related species but the MRLs recommended (by JECFA) differ, the most conservative set of Codex MRLs (i.e. the MRLs from the species associated with the lowest consumer exposure estimate) can be extrapolated to other related species (e.g. where different MRL values have been established for cattle and sheep and extrapolation is considered to goats, the lowest set of MRLs should be used for extrapolation).

***Explanatory note:** The fact that JECFA considered it appropriate to use identical M:T values in two related species provides grounds upon which to base the assumption that metabolism does not vary significantly within the group of related species—i.e. that the M:T established for the reference species can be applied to the concerned species.*

- (iii) Where the M:T established by JECFA is 1 in all tissues in a single reference species, the same Codex MRLs can be extrapolated to related species.

***Explanatory note:** The fact that the M:T is 1 in all tissues/food commodities indicates that the marker residue includes all the compounds of concern. It is considered reasonable to assume that this would also be the case in the concerned species.*

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<sup>1</sup> EHC 240 (1) defines the marker residue as: The parent drug, or any of its metabolites, or a combination of any of these, with a known relationship to the concentration of the total residue in each of the various edible tissues at any time between administration of the drug and the depletion of residues to safe levels. Where ‘total residues of toxicological concern’ are not defined, ‘total residue’ may be used where ‘Total residue’ is defined CXA 5-1993 (2): the total residue of a drug in animal derived food consists of the parent drug together with all the metabolites and drug based products in the food after administration of the drug to food producing animals. The amount of total residues is generally determined by means of a study using the radiolabelled drug, and is expressed as the parent drug equivalent in mg/kg of the food’.

Finally, while the above criteria can be used in all cases, the following additional criteria are proposed for fish, milk and eggs (i.e. extrapolation for fish, milk and eggs may be based on the above criteria OR based on the additional criteria below):

- (iv) For fish, where the MRL in muscle/fillet recommended by JECFA was established based on the limit of quantification (LoQ) (e.g., twice the LoQ), the Codex MRL can be extrapolated to all bony fish.

**Explanatory note:** *The fact that the MRL in muscle/fillet is below the LoQ indicates that residues in muscle/fillet are not measurable and so do not make a significant contribution to the intake calculation. Even if there are differences in metabolism between fish species, the possibility that they will be so dramatic as to result in a level of residues in muscle/fillet sufficiently high to significantly impact on overall consumer exposure is considered unrealistic.*

- (v) For milk and eggs, where the M:T established by JECFA is 1 (in milk or eggs of a reference species), the milk/egg Codex MRL of the reference species can be extrapolated to milk of other ruminants and eggs of other domesticated poultry species, respectively, even if the M:T is not 1 in tissues.

**Explanatory note:** *For milk and eggs, there may be a concern that the fat content differs between related species. However, if the M:T is 1 in the reference species this indicates that the M:T is not significantly influenced by the fat content.*

### A note on terminology

- 'Reference species' is used to refer to a species in which Codex MRLs have been established based on a scientific evaluation by JECFA
- 'Concerned species' is used to refer to a species for which extrapolation is being considered
- 'Related species' means species belonging to the same category of food producing species of ruminant and non-ruminant mammals\*, birds or fin fish\*\*
- 'Unrelated species' is used to refer to species belonging to different categories of food producing species

\* The category of non-ruminant food producing mammals is considered to include pigs, horses and rabbits

\*\* Three distinct classes of fish are usually identified: (i) jawless fish (Agnatha), (ii) cartilaginous fish (Chondrichytes) and (iii) finfish. To date, MRL data have been provided only for finfish, and it is these that are predominantly farmed and eaten. Consequently, it is proposed that MRL extrapolations in fish should be limited to this class.

\*\*\* Special attention should be paid to harmonizing the terminology used for the edible tissues.

### Reporting extrapolated MRLs

4. Where CCRVDF agrees to extrapolate MRLs, it should be clear that these MRLs were established by extrapolation rather than on the basis of a substance/species specific JECFA assessment. An appropriate symbol should be included next the relevant values reported in the MRL database. Moreover, extrapolated MRLs should be reconsidered in case the reference MRLs are modified or new data/information on the active substance in question becomes available.

### a) **Part B**

Amendment to paragraph 30 of the *Risk Analysis Principles Applied by the Codex Committee on Residues of Veterinary Drugs in Food*

(Consequential amendment for adoption)

A footnote in paragraph 30 of the Risk Analysis Principles – 2<sup>nd</sup> bullet point:

Approach for the extrapolation of MRLs of veterinary drugs to one or more species is presented in Annex C to these principles