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**Agenda Item 8** **CRD4**

**JOINT FAO/WHO FOOD STANDARDS PROGRAMME**

**CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS**

**26th Session**
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**Portland, Oregon, United States of America**

# REPORT OF THE PHYSICAL WORKING GROUP ON CRITERIA OR REQUIREMENTS FOR THE ESTABLISHMENT OF ACTION LEVELS FOR UNINTENDED AND UNAVOIDABLE CARRYOVER OF VETERINARY DRUGS FROM FEED TO FOOD OF ANIMAL ORIGIN

(Prepared by the Physical Working Group chaired by Australia and co-chaired by Canada)

## INTRODUCTION

1. A Physical Working Group (PWG) meeting chaired by Australia and co-chaired by Canada took place to further refine the discussion paper on the possible requirements or criteria for developing tolerance levels (action levels) for compounds in edible tissues/commodities due to the unintended and unavoidable carryover of authorized veterinary drugs in feed and their transfer from feed into food of animal origin and to use nicarbazin as a pilot case (Appendix I).

## WORK PROCESS: PARTICIPATION AND METHODOLOGY

2. The PWG was attended by various Member countries and organizations and observers.

3. The PWG Chairs discussed the last draft discussion document that was shared as part of CX/RVDF 23/26/8. In line with the terms of reference (TOR) of the PWG, the document contained proposed criteria for establishing action levels, a proposed procedure, as well as a pilot study estimating action levels for the unavoidable and unintended carry-over of nicarbazin in chicken eggs. Several comments were received on this draft as included in CX/RVDF 23/26/8 Add.1 , CRDs 6, 9 and 12.

4. On the basis of these comments, the PWG Chairs prepared a revised document, which is attached as an appendix to this report for consideration by Codex members and observers at CCRVDF26.

## SUMMARY OF DISCUSSION

5. The PWG chair provided an overview of the document and went through the 9 questions that were posed in the discussion paper included in CX/RVDF 23/26/8. The following were the main highlights of the discussion:

   a. With regards to comments on the General criteria, the working group, after fair bit of discussion, agreed to delete criteria #4 as it was redundant. Edits were made to criteria #2 to capture that the source of carryover should not result from the misuse of a veterinary drug.

   b. The inclusion of an option to use default levels of carry-over from medicated to unmedicated feed was specifically discussed as there were divergent views. While acknowledging that surveys of actual levels of carry-over from medicated to unmedicated feed are preferable, a number of members appreciated that extensive information is not always available and supported using default low levels of carry-over to estimate action levels as a pragmatic solution in the absence of better data. The PWG agreed to leave both choices as considerations rather than options. However, the section on default values of X % carry-over was left under square brackets to be discussed further at plenary.

   c. An additional consideration was included around importance of quality of the data being considered based on request from a member.

   d. The need to seek the advice of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) on the consumer safety of the proposed action level was also discussed. The additional contribution of carry-over to residues in edible commodities is low with some members suggesting the committee could utilise the TMDI approach to estimate the additional contribution while others proposed continuing current practice of seeking JECFA advice on dietary exposure.

e. Another point 3 e was added in the event information was not available for using the TMDI approach by JECFA and in that case alternative approaches could be used for determining the exposure assessment.

f. With regards to additional considerations that could be included, one member organization suggested to include the aspects on risks from development of antimicrobial resistance as part of the compounds being considered for this work.

g. A question was raised on how the proposed approach for setting action levels could be formalised, provided that it was agreed upon by CCRVDF26. The chair suggested that the proposed approach could be added as an annex to the Risk Analysis Principles Applied by the Codex Committee on Residues of Veterinary Drugs in Foods in the Procedural Manual. The PWG agreed to discuss this further at plenary.

**CONCLUSIONS**

6. The WG completed its task as per its TOR. The outcome is presented in the discussion paper attached in Appendix I.

7. The proposal for action levels put forward in the discussion paper aims to provide a pragmatic approach for the establishment of action levels. The criteria proposed (described in the discussion paper), which, when satisfied, supports the estimation of action levels while maintaining protection of the consumer. The use of this approach recognises that unavoidable and unintended carry-over of veterinary drugs from medicated to un-medicated feed occurs and sometimes leads to detectable residues in commodities currently without an MRL.

**RECOMMENDATIONS**

8. Codex members and observers are invited to consider:

i. the proposed approach for the establishment of action levels as presented in Appendix I, Part I <u>for comments and consideration by CCRVDF26</u>

ii. a pilot study using nicarbazin residues in chicken eggs, as presented in the discussion paper (CX/RVDF 23/26/8), which illustrates the proposed approach for estimating action levels as presented in Appendix I, Part II <u>for information to support comments on the proposed approach</u>

**APPENDIX I**

**PROPOSED APPROACH FOR ESTABLISHING ACTION LEVELS FOR VETERINARY DRUG RESIDUES IN FOOD PRODUCTS FROM NON-TARGET ANIMALS LINKED TO THE UNINTENDED AND UNAVOIDABLE VETERINARY DRUG CARRY-OVER IN NON-TARGET ANIMAL FEED**

**Introduction**

Action levels for unavoidable and unintended presence of veterinary drug residues in food products from non-target animals exposed to unavoidable and unintended veterinary drug carry-over in animal feed should be established based on a scientific risk assessment.

**DEFINITIONS**

**Action level:** An acceptable level of a veterinary drug residue in an animal food commodity produced from a non-target animal species, established to account for unavoidable and unintended veterinary drug carry-over in animal feed.

**Transfer Factor (TF):** The ratio between the veterinary drug residue in the tissue or commodity of interest (fat/skin, muscle, liver, kidney, milk or eggs) and the veterinary drug in the diet.

**Unavoidable and unintended veterinary drug carry-over in a non-target animal feed:** The presence of a veterinary drug in a non-target animal feed caused by the previous manufacture of medicated feed using the same equipment after one or more mitigation procedures have been performed (e.g., flushing, sequencing or physical clean-out).

**General criteria on the proposed approach**

1. Action levels for the unintended and unavoidable carry-over of veterinary drugs in non-target animal feed to food should only be derived where the framework of the Codex Code of Practice on Good Animal Feeding (CXC 54-2004), Good Manufacturing Practices (GMPs), and Hazard Analysis and Critical Control Point (HACCP) has been used to minimize the veterinary drug carry-over.
2. Action levels should be developed only to cover situations where low level residues of a registered veterinary drug are consistently detected by a national authority in edible commodities from non-target animals, and investigations by the national authority confirm the source to be unintended and unavoidable carry-over of a veterinary drug in animal feed and not due to misuse.
3. Action levels for non-target animals should be derived only for veterinary drugs that are authorized for use in a target-class of animal.
4. The residues in food resulting from the authorized or registered use of the veterinary drug plus the residues in food resulting from unavoidable and unintended veterinary drug carry-over in animal feed should not result in an exposure that exceeds the established Codex health-based guidance value (HBGV) for the veterinary drug.
5. Action levels should be derived only for residues of veterinary drugs that have adopted (or JECFA recommended) Codex maximum residue limits (MRLs).
    a) Action levels should not be established for veterinary drugs for which the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was unable to establish a health-based guidance value (HBGV) or recommend MRLs due to specific human health concerns or inadequate toxicological data.
6. Transfer factors (TFs) can be used to estimate the concentration of residues in edible commodities from non-target animals.
7. Action levels should be based on the amount of unintended and unavoidable veterinary drug in non-target animal feed after appropriate mitigation steps have been performed (*e.g.,* flushing, sequencing or physical clean-out) following the manufacture of feed containing the maximum authorised concentration of the drug for the target-class of animals.
8. Analytical methods should be available for the edible commodity for which action levels are being proposed.

**Procedure**

1. The following four steps should be followed for setting action levels for residues of veterinary drugs detected in foods of animal origin determined to be caused by unavoidable and unintended veterinary drug carry-over in non-target animal feed based on the Guidelines on the Application of Risk Assessment for Feed (CAC/GL 80-2013) and risk assessment approaches.

**Step 1. Animal dietary exposure assessment**

**Step 2. Estimates of anticipated residue levels in food commodities of animal origin**

**Step 3. Action levels**

**Step 4. Human dietary exposure assessment**

2. The CCRVDF will perform **Step 1**, **2** and **3** and then for **Step 4**, CCVRDF may request the JECFA conduct an appropriate exposure assessment based on the proposed action level derived under **Step 3**.

3. When CCVRDF requests such an exposure assessment from JECFA under **Step 4**, CCVRDF should:

   a) provide JECFA with the proposed action level(s) in the applicable commodity(ies) from **Step 1-3** and any data that might help with conducting an exposure assessment.

   b) request JECFA to conduct an exposure assessment that considers exposure from the proposed action level(s) and sources of exposure from the authorized use(s) of the veterinary drug.

   c) request JECFA to estimate an appropriate MR:TR ratio based on the established MR:TR ratios in the target animal species, applying safety factors as deemed necessary if a marker residue to total residues (MR:TR) ratio is not available for the affected commodity(ies).

   d) request JECFA if the exposure from residues in food resulting from the intended use of the veterinary drug plus the residues in food resulting from the proposed action level(s) exceeds the established Codex health-based guidance value (HBGV).

   e) In situations where radiolabeled residue data are not available to determine an MR:TR ratio, CCRVDF will ask JECFA to conduct a margin of exposure (MOE) assessment that accounts for the dietary exposure resulting from the established MRLs and the proposed action level. If CCRVDF determines that the MOE is sufficiently large, then CCRVDF moves forward with establishing the proposed action level.

4. Data such as residue transfer and residue monitoring data, from peer-reviewed scientific literature and/or previously reviewed by regulatory authorities, may be used in setting action levels for residues in food products from non-target animals, due to the unavoidable and unintended veterinary drug carry-over in non-target animal feed.

5. Residue monitoring data from a national authority, including trace-back data demonstrating that residues are caused by unavoidable and unintended veterinary drug carry-over in non-target animal feed, should be made available to CCRVDF to use these data to derive a proposed action level under **Step 3**.

6. Robust and good quality data are necessary to ensure that the action levels are representative of unavoidable and unintended carryover that occurs globally. CCRVDF may consider the following when evaluating the data:

   a. Do the data demonstrate that unavoidable and unintended carryover occurs even when mitigation steps are followed (e.g. flushing, sequencing)?

   b. Do the data demonstrate that unavoidable and unintended carryover concentrations of the veterinary drug in the non-target species' feed cause the presence of residues in edible commodities from non-target species?

   c. Are the data representative of the various formulations of the veterinary drug available globally?

   d. Are the data representative of feed mixing practices used globally?

7. The details of the four general steps for setting action levels for residues of veterinary drugs detected in foods of animal origin determined to be caused by unavoidable and unintended veterinary drug carry-over in non-target animal feed are discussed below.

**Step 1: Animal dietary exposure assessment**

a) The veterinary drug carry-over present in non-target feed or feed ingredients will be identified.

b) The anticipated exposure levels for non-target animals will be estimated considering:

- **[**Hypothetical carry-over rates of *x*% of the highest authorised dose of the veterinary drug in feed for the target animals (e.g., *x*% = 1%, 2.5%, 3% or 5%); and

- The expected concentration of unavoidable and unintended veterinary drug carry-over in non-medicated feed determined by feed mills operating under routine good manufacturing conditions (e.g., maximum observed concentration, median, or 95th percentile concentration of detected veterinary drug carry-over in surveys of feed or reported by feed mills).]

**Step 2: Estimates of anticipated residue levels in food commodities of animal origin**

**a) Calculating the Transfer Factors (TFs)**

The potential transfer of a veterinary drug from feed to food can be estimated by calculating TFs based on suitable feeding studies on non-target animals that were fed with feed containing the veterinary drug at levels close to the unavoidable and unintentional carry-over levels (e.g., feed, oral capsule).

TF can be calculated as follows:

$$\text{TF} = \frac{\text{residue level in edible animal commodity (milk, eggs or tissues) (fresh weight), expressed in mg/kg}}{\text{veterinary drug carry-over level in total feed ration (dry weight), expressed in mg/kg}}$$

**Notes:**

- The highest individual animal tissue residue level will be used in the TF calculations. If the highest residue was not reported the average residue will be used.
- In the case of residue levels that are below the limit of quantification of the analytical method (LOQ) and above the limit of detection (LOD) of the analytical method, the TF will be reported as LOQ ÷ feed concentration.
- In the case of residue levels that are below the LOQ will be used if residue values are between the LOD of the analytical method, and LOQ, but if residue values are less than the LOD, the data will not be used.
- If there are multiple feeding studies for a particular animal species, studies that fed the veterinary drug at concentrations most representative of the carry-over level should be used preferentially to calculate the TFs.
- If multiple TFs are derived from drug concentrations in feed close to the carry-over level, the median transfer factor will be used to estimate the anticipated residue levels in edible animal commodities.
- Survey/monitoring data from national regulatory bodies or reported in the scientific literature may be used to increase confidence in the estimated residue levels in edible tissues resulting from veterinary drug carry-over under good manufacturing practices.
- TFs should be calculated for one food commodity (e.g., liver) and should not be applied to a different commodity (e.g., eggs).
- TFs should be calculated for one species and should not applied to a different species.

**b) Calculating the anticipated veterinary drug transfer level**

Anticipated veterinary drug transfer levels in edible animal commodities (including muscle, liver, kidney, skin/fat, milk or egg) of non-target animals can be calculated using the TFs and the level of veterinary drug in the animal's feed estimated either by hypothetical carry-over rates of the highest authorised dose of the veterinary drug in feed for the target-class of animals or the maximum observed level or 95$^{th}$ percentile carry-over level as measured in non-medicated feed from feed mill studies operating under routine good manufacturing conditions.

Anticipated residue level = TF × veterinary drug carry-over level in animals total feed ration (dry weight)

**Step 3: Action levels**

Action levels for food commodities from non-target animals can be recommended based on the anticipated residue levels in food products from exposed animals under practical conditions and considering the potential utilization of available ADI for those veterinary drugs from the added exposure to the identified food commodities.

***Notes:***

TF based on a relatively high drug concentration in feed might overestimate the residue concentration in edible commodities caused by unavoidable and unintended veterinary drug carry-over in animal feed. To account for this, the anticipated residue level in edible commodities from non-target animals can be the lesser of either:

1. the concentration estimated by using the TF, or

2. the residue concentration determined to be caused by unavoidable and

unintended veterinary drug carry-over in animal feed that satisfied bullet point #2 of the General Criteria.

*"Action levels should be developed only to cover situations where low level residues of a registered veterinary drug are detected consistently by a national authority in edible commodities from non-target animals, and investigations by the national authority confirm the source to be unintended and unavoidable carry-over of a veterinary drug in animal feed".*

**Step: 4 Human dietary exposure assessment**

An estimate of consumer dietary exposure from residues present at action levels in food of animal origin (eggs, milk, meat, edible offal) from non-target animals will be calculated following approaches for both chronic exposure (based on the ADI) and acute exposure (based on the ARfD, when established).

***Notes:***

- In performing the dietary exposure assessment, exposure to the relevant foods containing residues at the proposed action level(s) and the other sources of dietary exposure from the authorized use(s) of the veterinary drug (e.g., exposure originating from the current Codex MRLs) should be considered.
- An estimate of the ratios for marker residues to total residues of toxicological or microbiological concern (MR:TR) may be required.
- Extrapolation of MR:TR ratios from one species to a related species (i.e., ruminant to ruminant) is likely feasible if:
    - Identical or very similar MR:TR ratios exist for tissues/commodities of two related species; and/or
    - The MR:TR ratios in tissues/commodities of one related species = 1.
- Dietary exposure estimates based on the intended use of the veterinary drug plus the residues in food resulting from the proposed action level(s) should not exceed the established Codex health-based guidance value (HBGV).
- Seek advice from JECFA if the exposure from residues in food resulting from the intended use of the veterinary drug plus the residues in food resulting from the proposed action level(s) exceeds the established Codex health-based guidance value (HBGV).