CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 8 **CRD24**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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REVISED 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

~~**Option 1:**~~

~~**Action level:** An [maximum tolerable] acceptable [safe] level [that does not pose [food safety risks]health risks] of a veterinary drug residue in food of animal origin an animal food commodity derived produced from a non-target animal beyond which unavoidable and unintended veterinary drug carryover in animal feed causes food safety risks species, established to account for unavoidable and unintended veterinary drug carry-over in animal feed beyond at which action should be taken if the level is above the action level. to manage risk.~~

Option 2:

Action Level: maximum concentration of residue resulting from unintended and unavoidable carryover in feed of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) ~~in feed~~ in~~to~~ a non-target animal that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food.

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 concentration of veterinary drug in animal feed~~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).

Non-target Animal: An animal that has been unintentionally exposed to a veterinary drug not authorized or registered for use in that animal species or production class.

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 be based on the ALARA principle and only be derived where the framework of the Codex Code of Practice on Good Animal Feeding (CXC 54-2004), Good Manufacturing Practices (GMPs), and/or Hazard Analysis and Critical Control Point (HACCP) ~~[insert reference]~~ 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 an approved/registered veterinary drug used according to good veterinary practices are consistently detected by a [competent ~~national~~] authority in edible commodities from non-target animals, and investigations by the [competent ~~national~~] authority confirm the source to be unintended and unavoidable carry-over of a veterinary drug in animal feed ~~and not due to its 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 in [edible commodities] should be [derived/calculated] from ~~based on~~ the transfer factors and concentration ~~and/or transfer factors~~ ~~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 veterinary drug residue in 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~~ [CCRVDF will do an initial TMDI calculation and where there are exceedances can request~~s~~ 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 consider conduct~~ing~~ 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 consider ~~estimate~~ estimating 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 to consider 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. [CCRVDF will use d~~D~~ata 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 [competent ~~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/or

- The expected concentration of unavoidable and unintended veterinary drug carry-over in non-~~medicated~~ target 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).] [investigations by the competent authority]

- ~~% ADI]~~

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:

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

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 residue transfer level

Anticipated veterinary drug residue transfer levels in ~~edible~~ food of animal origin ~~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 [and/or] 95th percentile carry-over level as measured in non-~~medicated~~ target feed from feed mill studies operating under routine good manufacturing conditions.

Step 3: Action levels

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

Action levels for food ~~of animal origincommodities~~ from non-target animals can be recommended based on the anticipated residue levels in food of animal origin ~~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 of animal origin~~commodities~~.

Notes:

TF based on a relatively high drug concentration in feed might overestimate the residue concentration in ~~edible commodities~~food of animal origin caused by unavoidable and unintended veterinary drug carry-over in animal feed. To account for this, the anticipated residue level in ~~edible commodities~~food of animal origin 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~~food of animal origin 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).]