ANALYSIS OF AGENDA ITEMS IN PREPARATION FOR THE 26th SESSION OF THE CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS (CCRVDF26)

13 to 17 February 2023

Portland, Oregon, United States of America

Agenda item 8: Criteria or requirements for the establishment of action levels for unintended or unavoidable carryover of veterinary drugs from feed to food of animal origin

Objective

This document offers a review and analysis of the agenda items planned for discussion at the 26th session of the **Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF)**, scheduled to take place face to face from 13 to 17 February 2023. This document is intended for possible use by the Codex communities of practice, promoted by GFoRSS and PARERA, as part of their contribution to enhancing awareness and supporting effective participation in international food standard setting meetings (Codex meetings) by representatives from members and observers.

The analysis provided in this document offers a factual review of select agenda items, their background, and a discussion of some considerations. This analysis is indicative in nature and does not represent an official position of the organizations mentioned above (PARERA and GFoRSS), their membership, or their management. It provides a synthesis and analysis of the work currently under discussion by the CCFA, which may be useful for delegations from Codex delegations, part of the GFoRSS Network Community, to prepare their positions considering the needs and specificity of the region and the potential impact of the proposed food standards.

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**It is important to note that experts – members of Expert Working Groups – do not represent the organizations and / or jurisdictions to which they are affiliated. The selection and participation in Expert Working Group proceedings is based on each expert's own credentials and experience, which should not be misconstrued as the country's / delegation's / organization's position to which they belong.*

Agenda item 8 : Criteria or requirements for the establishment of action levels for unintended or unavoidable carryover of veterinary drugs from feed to food of animal origin

Document

CX/RVDF 23/26/8

Background

The issue of veterinary drug residues in animal feed and food has long been raised because of human, animal and environmental health concerns related to direct exposure to these residues. In this context, the Codex Alimentarius Commission was requested to revise and update the Codex Code of Practice on Good Animal Feeding (CXC 54-2004) to address emerging hazards arising from the use of feed and products derived from highly utilized feed production technologies.

In order to establish appropriate management measures regarding the problem of unavoidable and accidental transfer of veterinary drugs from feed to a non-target animal, the CCRVDF decided to initiate work and discussions on the possibility of defining criteria/requirements for the establishment of action levels for residues of veterinary drugs in foods of animal origin resulting from such transfer.

At the 22nd Session of the CCRVDF, an Electronic Working Group (EWG), co-chaired by the United States of America and Canada, was tasked with preparing the discussion paper for consideration by the 23rd Session of the CCRVDF[1] on the unintentional presence of veterinary drugs in food due to the transfer of veterinary drugs in animal feed. To this end, an online forum was made available to countries to provide answers to the various questions raised on the subject including the scope of the project, the relevant data required and the need to establish a specific standard considering existing policies/guidelines/codes of practice.

At the 23rd Session of the CCRVDF[2], the EWG presented a summary of the key discussion points contained in CRD2, and its main recommendations are as follows: i) The management of unavoidable and unintended presence of residues of approved veterinary drugs in food as a result of transfer of veterinary drugs into animal feed is covered by the Code of Practice on Good Animal Feeding (CAC/RCP 54-2004); ii) Development of risk management recommendations to minimize the unavoidable and unintentional presence of residues of approved veterinary drugs in food as a result of the transfer of veterinary drugs into animal feed; and iii) Identification of relevant issues for scientific evaluation by FAO and WHO (including a case study of a particular veterinary drug/food commodity pair, namely Lasalocid sodium in eggs).

Based on the discussion, the Committee agreed with the criteria established by the EWG for requesting risk management recommendations/measures and the general considerations for such recommendations/measures as proposed in the EWG's report. A request for scientific advice was sent to FAO and WHO to test the criteria for requesting risk management measures/recommendations and general considerations for risk management measures/recommendations and to use Lasalocid sodium in eggs as a case study.

At the 25th Session of the CCRVDF[3], FAO and WHO presented their scientific advice from the Joint FAO/WHO Expert Meeting on Unavoidable and Incidental Transfer of Veterinary Drug Residues from Animal Feed to Food[4] (summary of the FAO/WHO report is presented below).

The experts raised the importance of efforts to reduce and avoid hazards associated with the transfer of veterinary drugs for the safety of food for human consumption.

[1] CX/RVDF 16/23/7, September 2016.
[2] REP17/RVDF
[3] REP21/RVDF
[4] CX/RVDF 21/25/3-Add.1

They also pointed out the recent revision of the manual entitled Good Practices for the Animal Feed Industry - Implementation of the Codex Alimentarius Code of Practice on Good Animal Feeding published by FAO and IFIF in 2020, which includes guidance on transfer.

With respect to the Codex Code of Practice on Good Animal Feeding, the CCRVDF 25 considered that the provisions of the Code of Practice provided sufficient guidance to Codex members to manage the issue of unavoidable and accidental transfer of residual levels of veterinary drugs from animal feed to human food. Therefore, no further action by the CCRVDF would be required at this time regarding the Code of Practice on Good Animal Feeding (CXC 54-2004).

With regard to action levels, the CCRVDF25 agreed that the Committee could consider establishing such levels in the future as appropriate, provided that good animal feeding practices were applied in accordance with the Code of Practice on Good Animal Feeding (CXC 54-2004).

The CCRVDF25 agreed to establish an electronic working group, chaired by Australia and co-chaired by Canada, to (i) prepare a discussion paper on criteria or requirements for the development of action levels for foods derived from non-target animals to address the unavoidable and adventitious transfer of veterinary drugs from animal feed; and (ii) conduct a pilot study on the establishment of action levels for Nicarbazine in food products derived from non-target animals (e.g., action levels for nicarbazine in chicken eggs), resulting from the unavoidable and adventitious transfer of nicarbazine in non-target animal feed.

SUMMARY OF PROPOSALS AND ADVICE FROM THE JOINT FAO/WHO MEETING

JECFA concluded that ensuring the safety of animal feed is an important key element to support the efforts to reduce and avoid hazards associated with the transfer of veterinary drugs for food safety. The specific risk management solutions proposed included:

Code of Practice for Good Animal Feeding (CXC 54-2004)

1. Increase awareness and provide readily available information on the possible implications of transfer resulting from the use of authorized veterinary drugs.

2. To strengthen national capacity to implement the Codex Code of Practice on Good Animal Feeding and related measures in the context of animal feed production.

3. To emphasize the importance of establishing, where possible, separate and dedicated production lines for medicated feed.

4. Encourage prescribers and users of medicated feeds to consider appropriate selection of approved veterinary drugs (including active ingredients, formulation, and dosage form) to achieve desired therapeutic outcomes while taking into consideration the implications of transfer.

5. Emphasize the importance of monitoring and control of feed materials.

6. Emphasize the avoidance of the routine use of medicated feeds by implementing the use of healthy animal practices and ingredients.

7. Include specific guidance in the Codex Code of Practice for Good Animal Feeding on HACCP control points identified for transfer during transport from the feed mill to the farm.

Action levels

1. Definition of an acceptable amount of veterinary drugs based on residue tolerances (e.g., MRLs) in food products produced from exposed animals. This approach works as long as the transferred veterinary drug has established MRLs in non-target species exposed to it. For many veterinary drugs added to feed, MRLs for non-target species/products have not been established, so other methods must be used to define acceptable levels of carryover.

2. Establishment of action levels for veterinary drug residues in food. These action levels would set a regulatory limit below which no further enforcement action would be required. The definition of these action levels should be based on a documented risk assessment, considering the following elements

- ✓ Transfer of veterinary drugs into feed or presence of drug residues in feed ingredients.
- ✓ Identification of the level of action in feed for non-target species.
- ✓ Definition of transfer factors from feed to food.
- ✓ Definition of the action level for food products from non-target species.

3. The intended use of a veterinary drug in addition to the incidental use of the drug should not result in exposures exceeding the health-based reference values (SBVs).

At the 26ème session of the CCRVDF[5], the working document of the EWG will be presented to delegates and different proposals will be discussed, which include the proposal approach for the establishment of action levels for veterinary drugs in food from non-target animals, resulting from the unavoidable and accidental transfer of veterinary drugs in food intended for non-target animals and the pilot study estimating action levels for the unavoidable and accidental transfer of Nicarbazine in chicken eggs.

In addition, the CCRVDF26 should also consider the following additional issues identified by the EWG:

- ❖ What approach should be used to estimate the level of transfer of veterinary drugs in feed that are not intended for target animals where residues (of the veterinary drug) are not expected to appear in the target animals (e.g., assumed transfer rates, highest residue levels in feed produced in feed mills, etc.)?
- ❖ What assumptions should be made when calculating TFs?
- ❖ How much emphasis should be placed on follow-up data when relevant follow-up data are available?
- ❖ What approach should be taken to determine an appropriate MR:TR ratio (marker residue/total residue of toxicological or microbiological concern) when no specific radiolabeled data exist for dietary exposure due to transfer of veterinary drugs?
- ❖ Are there other considerations that were not considered in this risk assessment procedure?
- ❖ Are the proposed roles and responsibilities appropriate in establishing levels of action?

Analysis

15 Member countries and one observer participated to the work of the EWG. The draft document of the EWG was circulated twice to delegates for their comments and suggestions. During the discussion, there were two main areas of divergent views:

1. The inclusion of an option to use default levels of carry-over from medicated to unmedicated feed:

   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 the option of using default low levels of carry-over to estimate action levels as a pragmatic solution in the absence of better data.

2. 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:
   Some members suggested that the committee could utilise the Theoretical Maximum Daily Intake (TMDI) approach to estimate the additional contribution while others proposed continuing current practice of seeking JECFA advice on dietary exposure.

Key EWG outputs related to the proposed approach for the establishment of action levels and the pilot study are presented below:

[5] CX/RVDF 23/26/8

PROPOSED APPROACH FOR ESTABLISHING ACTION LEVELS FOR VETERINARY DRUGS IN FOOD FROM NON-TARGET ANIMALS RESULTING FROM UNAVOIDABLE AND ACCIDENTAL TRANSFER OF VETERINARY DRUGS IN FOOD TO NON-TARGET ANIMALS

I. GENERAL CRITERIA

1. Action levels should only be used as a basis when the framework defined in the Code of Practice for Good Animal Feeding (CXC 54-2004), Good Manufacturing Practices (GMP) and Hazard Analysis Critical Control Point (HACCP) minimizes the transfer of veterinary drugs.

2. Action levels should only be used to cover situations where low levels of residues of approved veterinary drugs are detected consistently by a national authority in edible products from non-target animals, and where studies conducted by the national authority confirm that the source is an unavoidable and accidental transfer of veterinary drugs in feed.

3. Action levels for non-target animals should be established only when veterinary drugs are authorized for use in a target animal class.

4. No action levels for non-target animals should be developed when the use of veterinary drugs is not authorized/approved.

5. Residues in food resulting from authorized or registered use of the veterinary drug and residues in food resulting from the unavoidable and accidental transfer of the veterinary drug in feed should not result in an exposure exceeding the health reference value (HRV) established for that veterinary drug.

6. Action levels should only be established for veterinary drug residues that meet Codex (or JECFA recommended) maximum residue limits (MRLs).

a) No action level should be established for veterinary drugs for which the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has been unable to establish a health reference value (SRV) or recommend an MRL due to specific human health concerns or inadequate toxicological data.

7. Transfer factors (TFs) can be used to estimate the concentration of residues in edible products from non-target animals.

8. Action levels should be based on the unavoidable and incidental amount of veterinary drugs in non-target animal feeds after appropriate mitigation steps (e.g., rinsing, sequencing, or physical clean-up), following the manufacture of feeds containing the maximum allowable concentration of drugs for the target animal class.

9. Analytical methods should be available for the edible product for which action levels are proposed.

II. PROPOSED PROCEDURE

The procedure is based on the following four steps:

Step 1. Animal Dietary Exposure Assessment (to be conducted by CCRVDF as part of an EWG)

- Identify the transfer of veterinary drugs in foods or feed ingredients to non-target animals;
- Estimate anticipated exposure levels for non-target animals, considering the following:

Option 1 - **Assumed transfer rates of x%** of the highest permitted dose of the veterinary drug in feed for target animals (e.g., x% = 1%, 2.5%, 3% or 5%).

Option 2 - **The expected concentration of unavoidable and incidental transfer of veterinary drugs** in non-medicated feeds as defined by feed mills typically operating under good manufacturing conditions (e.g., maximum observed concentration, median concentration, or 95th percentile concentration of detected veterinary drug transfer based on animal feeding studies or feed mills).

Step 2. Estimates of anticipated residue levels in food products of animal origin (to be conducted by CCRVDF under an EWG);

a. **Calculation of transfer factors (TFs**) according to the formula below, based on appropriate feeding studies of non-target animals with feed containing said veterinary drug at levels close to unavoidable and incidental transfer.

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

b. **Calculation of the anticipated residue level** using TFs and the level of transfer of the veterinary drug to the feed, estimated either through (Option 1) hypothetical transfer rates of the highest permitted dose of the veterinary drug in feed for the target class of animals or (Option 2) the maximum observed level or 95th percentile transfer level, as measured in non-medicated feeds, from studies of feed mills typically operating under good manufacturing conditions.

$$\text{Anticipated residue level} = TF \times \text{veterinary drug carry-over level in animals total feed ration (dry weight)}$$

Step 3. Action Levels (to be completed by CCRVDF as part of an EWG);

Recommendation of action levels for food products from non-target animals based on anticipated residue levels in food products from exposed animals under practical conditions, and considering the potential use of the available ADI for these veterinary drugs resulting from additional exposure to identified food products.

Step 4. Human dietary exposure assessment (to be performed by JECFA upon request from CCRVDF, based on the evidence established in the previous steps including the proposed action levels from Step 3).

Estimation of consumer dietary exposure to residues at action levels in food (eggs, milk, meat, edible offal) derived from animals based on chronic exposure (based on the Acceptable Daily Intake (ADI)) and acute exposure (based on the Acute Reference Dose (ARfD), where defined) used by JECFA.

In this context, JECFA should:

i) conduct an exposure assessment that considers exposure from the proposed action level(s) as well as sources of exposure from the authorized use(s) of the veterinary drug;
ii) estimate an appropriate marker residue to total residue (MR:TR) ratio, based on the MR:TR ratios established in the target animal species, applying the required health safety factors if an MR:TR ratio was not available for the affected commodity(ies); and
iii) Define rule on exposure from residues in food that result from the intended use of the veterinary drug as well as residues in food that result from the proposed action level(s) exceeds the established health reference value (HRV).

PILOT STUDY ESTIMATING ACTION LEVELS FOR UNAVOIDABLE AND ACCIDENTAL TRANSFER OF NICARBAZIN TO CHICKEN EGGS

Nicarbazin, a coccidiostat drug used in broiler chickens, was studied by the EWG as part of the pilot study. Nicarbazin is an equimolar mixture of 4,4'-dinitrocarbanilide (DNC) and 2-hydroxy-4,6-dimethylpyrimidine (HDP). After oral ingestion, the complex dissociates to two major metabolites, DNC and HDP and both components undergo metabolism via different routes and at different rates.

The different steps of the proposed action level approach were followed and used to propose the appropriate action level.

A summary of the steps followed is presented below.

Step 1. Dietary exposure assessment in animals

- Option 1: Transfer of nicarbazin to feed for laying hens at hypothetical levels of 1%, 2.5%, 3%, and 5% of the maximum allowable level of 125 mg/kg for broilers would result in transfer levels of nicarbazin to feed for laying hens of 1.25, 3.125, 3.75 and 6.25 mg/kg, respectively.
- Option 2: Table 1 summarizes the levels of transfer of nicarbazin to non-medicated feed during the manufacture of medicated feed. Studies were consulted to support the data considered.

Table 1: Data considered related to the levels of transfer

Level in medicated feed (mg/kg)	Flushing procedure	Level in flush (mg/kg)	Level in non-medicated diet (mg/kg)	Reference
125	Five flush size treatments 2.5, 5.0, 10, 15, and 20% of the mixer's total capacity (Forberg 454.5 kg capacity drop bottom paddle mixer)	 19.2 14.8 12.0 6.5 5.6	 1.8 2.1 2.2 1.4 1.5	Martinez et al., 2018
125	Three sequential 3-tonne cleaning batches, sampling before pelleting and at one point post-pelleting		Pre-pelleting (first tonne milled) - 3.4 ± 0.26 Post pelleting (after 8 tonnes) - 7.2± 1.29	McEvoy et al., 2003

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

1. TF calculation for eggs

Feeding studies of laying hens fed only diets containing nicarbazin levels near the transfer level of 2.2 mg/kg evaluated the potential for transfer of veterinary drugs from feed to eggs. The TFs for eggs were 0.051 and 0.150. Therefore, the median TF was 0.10.

2. Calculation of the anticipated level of transfer of veterinary drugs in eggs

- Option 1: Residues of DNC in egg were calculated to be equivalent to 61.5, 158, 190 and 318 µg/kg and would be expected to transfer to feed at 1, 2.5, 3 and 5% of the maximum permitted level of 125 mg/kg.
- Option 2: Based on studies of feed mills under practical conditions, the maximum transfer of nicarbazine into non-medicated feed is 2.2 mg/kg (Martinez et al., 2018). Thus, the expected nicarbazine residue level in eggs would be 220 µg/kg (TFegg × residue level in feed = 0.10 × 2.2 mg/kg feed).

Step 3. Action levels

In the example studied, the anticipated nicarbazin residue level of 220 µg/kg was chosen as the value to be used in the human exposure assessment based on feed mill studies (Option 2). A summary of the residue levels identified in chicken eggs for nicarbazin are presented in the table 2.

Table 2: Summary of anticipated residue levels in chicken eggs

Commodity	TF	Anticipated residue level (µg/kg)				
		Option 1				Option 2
		1% (1.25 mg/kg feed)	2.5% (3.125 mg/kg feed)	3% (3.75 mg/kg feed)	5% (6.25 mg/kg feed)	2.2 mg/kg feed
Egg	0.10	125	312.5	375	625	220

Step 4. Human dietary exposure assessment

For expected transfer residues in eggs, a dietary exposure assessment was based on the nicarbazin residue level of 220 µg/kg in eggs, a food consumption factor of 100 g of eggs and an ADI of 900 µg/kg bw/day (Table 4).

Since no marker residue to total residue (MR:TR) ratio is available for eggs, the lowest MR:TR ratio identified by JECFA in the target animal species (kidney - 0.25) was used to perform the human dietary exposure assessment.

Dietary exposure estimate (TMDI) = 0.088 mg ÷ 60 kg person/day = 0.000147 mg/kg bw/day = 0.00147 mg/kg bw/day ÷ 0.9 mg/kg bw/day × 100% = 0.16% of ADI

Table 3: Dietary exposure estimates for nicarbazin residues (DNC) in hen eggs using the JECFA TMDI approach.

Produit	Consommation quotidienne (g)	Niveau de résidu anticipé (µg/kg)	MR:TR	AJMT (mg)
Œuf	100	220	0,25	0,088
AJMT en tant que pourcentage de DJA				0,16 %

PROPOSED ACTION LEVEL FOR NICARBAZIN IN CHICKEN EGGS:

It is proposed to establish an action level of 0.220 mg/kg for nicarbazin in eggs from laying hens considered as non-target animals, to consider the presence of nicarbazin resulting from unavoidable and accidental transfer of nicarbazin in feed (Table 4). This proposal is in line with similar limits established by the EU and New Zealand for nicarbazin in eggs (0.220 mg/kg).

Table 4: Proposed action level for nicarbazin in chicken eggs

Produit	Niveau d'action proposé (mg/kg)	[Pour comparaison] Contenu maximal (mg/kg)
Œuf	0,220	0,3 (UE) 0,3 (Nouvelle-Zélande)
Résidu marqueur – 4,4'-dinitrocarbanilide (DNC)		

Conclusion and recommendations

The pilot study on nicarbazin residues in chicken eggs illustrates the proposed approach to estimate action levels and provides support for the observations on the proposed approach.

The example studied confirms that unavoidable or accidental transfer of veterinary drugs from medicated feed to non-medicated feed can occur and result in detectable residues in commodities requiring the establishment of MRLs.

Regulators should pay particular attention to the problem of transfer of veterinary drug residues via animal feed. The origins of this contamination may be diverse due to the constant development of new technologies to use potential sources of animal feed: such as feed made from crops fertilized with bio-waste (manure harvested from treated animals), use of antimicrobial agents in fermentation products, such as DDS, and the natural presence of some antibiotics produced by organisms in the environment.

Competent authorities should consider a risk management approaches to address similar incident of unintended transfer of residues of vet drugs based on the methodology presented in the discussion paper.