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CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 8 **CX/RVDF 24/27/8**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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CRITERIA AND PROCEDURES FOR THE ESTABLISHMENT OF ACTION LEVELS FOR VETERINARY DRUGS IN FOOD OF ANIMAL ORIGIN RESULTING FROM UNAVOIDABLE AND UNINTENTIONAL VETERINARY DRUG CARRY-OVER IN NON-TARGET ANIMAL FEED

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

Codex members and observers wishing to submit comments on the recommendations presented in paragraph 10 and Appendices I and III should do so as instructed in CL 2024/68-RVDF available on the Codex webpage/Circular Letters[1] or CCRVDF/Related Circular Letters[2]

INTRODUCTION

1. An Electronic Working Group (EWG) chaired by Australia and co-chaired by Canada was re-established[3] to further develop the criteria and procedures for establishing action levels based on discussions at the 26th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF26, 2023). The EWG also sought to revisit the nicarbazin pilot and consider other veterinary compounds (Appendix I).

WORK PROCESS: PARTICIPATION AND METHODOLOGY

2. The EWG registered 45 Member countries and observer organizations to participate in this work. The List of Participants is presented in Appendix IV.

3. The EWG Chairs circulated the first draft document to the EWG members on 6th October 2023 in Eng. In line with the terms of reference (ToR) of the EWG, the proposed criteria for establishing action levels and proposed procedures were updated in line with the discussions held at CCRVDF26. The pilot study estimating action levels for unavoidable and unintentional carry-over in chicken eggs expanded to include nicarbazin and lasalocid. Two EWG members (the Republic of Korea and the United States of America) and one observer organization (IFIF) provided comments on this draft.

4. Based on these comments, the EWG Chairs finalized the discussion paper and submitted it to the Codex Secretariat for consideration by Codex members and observers.

SUMMARY OF DISCUSSION

5. The comments received revealed two main areas of divergent views on the draft discussion paper:

    i. The use of default hypothetical carry-over levels from medicated to unmedicated feed was questioned. The EWG chairs acknowledge that global surveys of actual carry-over levels from medicated to unmedicated feed are preferable. However, this information is not available, so using a default low level of carry-over to estimate action levels is a pragmatic solution without better data.

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1 http://www.fao.org/fao-who-codexalimentarius/resources/circular-letters/en/

2 http://www.fao.org/fao-who-codexalimentarius/committees/committee/related-circular-letters/en/?committee=CCRVDF

3 REP23/RVDF26, para. 102

ii. 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 not agreed upon. The EWG Chairs note that the additional contribution of carry-over to residues in edible commodities and resulting consumer exposure is low. As proposed in the paper, the Committee could utilize the Theoretical Maximum Daily Intake (TMDI) approach to estimate the additional contribution and seek the advice of JECFA if an issue with dietary exposure is identified.

6. The United States of America has proposed an alternative management approach to deal with residues resulting from unavoidable and unintentional carry-over instead of setting action levels (Appendix III).

CONCLUSIONS

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

8. The proposal in the discussion paper aims to provide a pragmatic approach for establishing action levels. When satisfied, the pragmatic criteria proposed (described in Appendix I) support the estimation of action levels while maintaining consumer protection. This approach recognizes that the unavoidable and unintended carry-over of veterinary drugs from medicated to un-medicated feed occurs and sometimes leads to detectable residues in commodities without an MRL.

9. One member submitted an alternative proposal for dealing with residues in food of animal origin resulting from unavoidable and unintentional carry-over. The alternative approach, however, would provide a different certainty for trade than action levels. The alternative approach is included in Appendix III for completeness.

RECOMMENDATIONS

10. CCRVDF is invited to consider the recommendations below based on comments submitted by Codex Members and Observers in reply to CL 2024/68-RVDF as follows:

i. The proposed approach to establishing action levels as presented in Appendix I (for comments).

Pilot studies using nicarbazin and lasalocid residues in chicken eggs illustrate the proposed approach for estimating action levels. Appendix II provides data/information to support and inform comments on the proposed approach presented in Appendix I.

ii. The alternative approach submitted by the United States of America as presented in Appendix III (for comments).

iii. Should Codex members support the approach proposed by the EWG in Appendix I, consider whether the action levels proposed for nicarbazin and lasalocid in eggs in Appendix II, Part I/Table 7 y and Part II/Table 14 could be submitted for adoption by the 47th Session of the Codex Alimentarius Commission (CAC47) which are reproduced below for convenience:

Proposed action level for nicarbazin in chicken egg

Commodity	Proposed action level (mg/kg)	Notes
Egg	0.220	Marker residue - 4,4'-dinitrocarbanilide (DNC)

Proposed action level for lasalocid in chicken egg

Commodity	Proposed action level (mg/kg)	Notes
Egg	0.1	Marker residue – Lasalocid A

APPENDIX I

ESTABLISHMENT OF ACTION LEVELS FOR VETERINARY DRUGS IN FOOD OF ANIMAL ORIGIN RESULTING FROM UNAVOIDABLE AND UNINTENTIONAL VETERINARY DRUG CARRY-OVER IN NON-TARGET ANIMAL FEED

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

Proposal by the Electronic Working Group

(For comments)

DEFINITIONS AND TERMS USED IN THIS DOCUMENT

Action level: Maximum concentration of residue resulting from unintended and unavoidable carry-over in a feed of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) in 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.

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 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 unintentionally exposed to a veterinary drug not authorized or registered for use in that animal species or production class.

1. Action levels for unavoidable and unintended presence of veterinary drug residues in food products from non-target animals exposed to veterinary drug carry-over in animal feed will be established based on a scientific risk assessment taking into account food safety and whether the best practice has been followed (e.g., *Code of Practice on Good Animal Feeding* (CXC 54-2004), Good Manufacturing Practices (GMP) and Hazard Analysis and Critical Control Point (HACCP)) to minimize the unavoidable and unintended veterinary drug carry-over in non-target animal feed, to a level that is achievable after having implemented mitigation measures according to the Code of Practice on Good Animal Feeding.

General criteria for the proposed approach

2. Action levels for the unintended and unavoidable carry-over of veterinary drugs in non-target animal feed to food should be based on the 'As Low as Reasonably Achievable' concept and only be derived where the framework of the *Code of Practice on Good Animal Feeding*, GMPs, and/or HACCP has been used to minimize the veterinary drug carry-over.

3. 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] authority in edible commodities from non-target animals and investigations by the [competent] authority confirm the source to be unintended and unavoidable carry-over of a veterinary drug in animal feed.

4. Action levels for non-target animals should be derived only for veterinary drugs authorized for use in a target class of animals.

5. 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 health-based guidance value (HBGV) for the veterinary drug.

6. Action levels should be derived only for residues of veterinary drugs that have adopted (or JECFA recommended) 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 an HBGV or recommend MRLs 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 commodities from non-target animals.]

8. Action levels in [edible commodities] should be [derived/calculated] from the transfer factors and concentration of unintended and unavoidable veterinary drugs 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 authorized concentration of the drug for the target class of animals.

9. Analytical methods should be available for the veterinary drug residue in the edible commodity for which action levels are proposed.

Procedure

10. 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 (CX/G 80-2013) and risk assessment approaches.

Step 1. Assess animal dietary exposure assessment.
Step 2. Estimate anticipated residue levels in food commodities of animal origin.
Step 3. Set Action levels.
Step 4. Evaluate human dietary exposure assessment.

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

12. [CCVRDF will do an initial Theoretical Maximum Daily Intake (TMDI) calculation, and where there are exceedances, can request 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 **Steps 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 consider estimating an appropriate Marker Residue (M): Total Residues of toxicological concern (T) ratio based on the established M:T ratios in the target animal species, applying safety factors as deemed necessary if a M:T ratio is not available for the affected commodity(ies).

    d) request JECFA to consider if the exposure to 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 health-based guidance value (HBGV).

    e) In situations where radiolabelled residue data are not available to determine an M:T 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.]

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

14. Residue monitoring data, including trace-back information from a [competent authority], demonstrating that residues are caused by unavoidable and unintended veterinary drug carry-over in non-target animal feed, should be made available to CCRVDF.

15. CCRVDF may consider the following when evaluating the data:

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

    b) Does the data demonstrate that unavoidable and unintended carry-over concentrations of the veterinary drug in the feed of non-target animals cause residues in edible commodities from non-target animals?

    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?]

16. 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: Assess animal dietary exposure assessment.

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

18. The anticipated exposure levels for non-target animals will be estimated considering:

    a) **Option 1**: A default hypothetical carry-over of 1% can be applied to the highest authorized dose of the veterinary drug in feed for the target class of animals in situations where:

        i) Unintended and unavoidable carry-over has been demonstrated; and

        ii) Suitable data is not available to establish with certainty that unintended and unavoidable carry-over would occur at a level higher (or lower) than 1%.

    b) **Option 2**: The maximum observed concentration of unavoidable and unintended veterinary drug carry-over in non-target feed determined in feed mills operating under routine good manufacturing conditions. Monitoring data where investigations cannot verify GMP is unsuitable for this purpose.

Step 2: Estimate anticipated residue levels in food of animal origin.

a) Calculating the Transfer Factors (TFs)

19. 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 fed feed containing the veterinary drug at levels close to the unavoidable and unintentional carry-over levels (e.g., feed, oral capsule).

20. TF can be calculated as follows:

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

Notes (1):

1. The highest individual animal tissue residue level will be used in the TF calculations. The average residue will be used if the highest residue is not reported.
2. 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.
3. Residue values ~~are~~ less than the LOD of the analytical method will not be used.
4. 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.
5. 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.
6. 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.
7. TFs should be calculated for one food commodity (e.g., liver) and should not be applied to a different commodity (e.g., eggs).
8. TFs should be calculated for one species and should not be applied to a different species.

b) Calculating the anticipated veterinary drug residue transfer level.

21. Anticipated veterinary drug residue transfer levels in food of animal origin (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 authorized dose of the veterinary drug in feed for the target-class of animals or the maximum observed carry-over level as measured in non-target feed from feed mills operating under routine good manufacturing conditions. Monitoring data where investigations cannot verify GMP is unsuitable for this purpose.

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

Step 3: Action levels

22. Action levels for food of animal origin from non-target animals can be estimated based on the anticipated residue levels in food of animal origin from animals exposed under practical conditions.

Notes (2):

TF based on a relatively high drug concentration in feed might overestimate the residue concentration in 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 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 an approved/registered veterinary drug used according to good veterinary practices are consistently detected by a [competent] authority in edible commodities from non-target animals, and investigations by the [competent] authority confirm the source to be unintended and unavoidable carry-over of a veterinary drug in animal feed".

[Step: 4 Human dietary exposure assessment

23. 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 (3):

1. 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.
2. An estimate of the ratios for marker residues to total residues of toxicological or microbiological concern (M:T) may be required.
3. Extrapolation of M:T ratios from one species to a related species (i.e., ruminant to ruminant) is likely feasible if:
    a) Identical or very similar M:T ratios exist for tissues/commodities of two related species; and/or
    b) The M:T ratios in tissues/commodities of one related species = 1.
4. 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 health-based guidance value (HBGV).
5. 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 health-based guidance value (HBGV).]

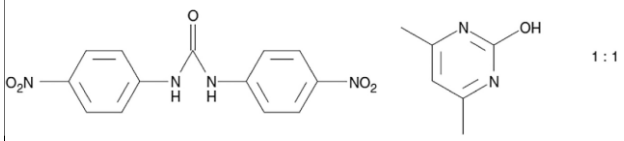
APPENDIX II

(For information to support comments on Appendix I)

PILOT STUDY A:
ESTIMATING ACTION LEVELS FOR UNAVOIDABLE AND UNINTENTIONAL NICARBAZIN CARRY-OVER IN CHICKEN EGG

1 Nicarbazin is a non-ionophoric coccidiostat administered in feed to broiler chickens to prevent and control coccidiosis caused by *Eimeria* spp. Nicarbazin is an equimolar mixture of 4,4'-dinitrocarbanilide (DNC) and 2-hydroxy-4,6-dimethylpyrimidine (HDP). DNC is also known as N,N'- bis(4-nitrophenyl urea) and 1,3-bis(4-nitrophenyl urea). After oral ingestion, the complex dissociates into two major metabolites, DNC and HDP, and both components undergo metabolism via different routes and at different rates. **Table 1** gives a summary of nicarbazin details.

Table 1: Summary of nicarbazin details

Chemical name	an equimolar amount of 4,4'-dinitrocarbanilide (DNC) and 2-hydroxy-4,6-dimethylpyrimidine (HDP). DNC is also known as N,N'-bis(4-nitrophenyl)urea.
Marker residue	4,4'-dinitrocarbanilide (DNC)
Structure	DNC HDP  1 : 1 (Tarbin et al., 2005)
Water solubility (20 °C)	DNC - 0.02 mg/L and HDP >10000 mg/L
log K_{ow}	DNC - 3.6 and HDP - 0.94 at pH 5-9 (EFSA, 2003).
Target animal	chickens for fattening, turkeys for fattening
Authorized maximum content in complete feed and Withholding Period (WHP)	125 ppm in the feed, 1 day 40-50 ppm, 0 days (nil) when co-formulated with ionophores (AUS) <125 ppm with 4 days, >125 ppm with 5 days (US) 30-50 ppm with 0 days when co-formulated with narasin (US) 125 ppm, 1 day (EU), 40-50 ppm, 5 days when co-formulated with narasin (EU)
LOQ	0.02 - 0.1 mg/kg for all tissues
ADI	0.9 mg/kg bw (DNC) (JECFA/94/SC, 2022)
MRLs for chicken (broilers) (mg/kg)	***AUS*** muscle 5, liver 35, kidney 20, fat/skin 10, egg 0.3 ***EU*** muscle 4, liver 15, kidney 6, fat/skin 4 ***Canada*** muscle 4, liver 15, kidney 8, fat/skin 4 ***Codex*** muscle 0.2, liver 0.2, kidney 0.2, fat/skin 0.2 **JECFA (2022)** muscle 4, liver 15, kidney 8, fat/skin 4 ***US*** liver 52 ***UK VMD*** egg 0.100 (Differential Action Limit, DAL)
Maximum content in feed for non-target species (mg/kg)	***EU Regulation EU 574/2011*** Feed materials- 1.25 Compound feed for equine species, laying birds and chickens reared for laying (> 16 weeks) – 1.25, other animal species – 3.75 ***Brazilian Regulation*** (***MAPA 2016)*** Feed materials - 1.25

Maximum content in food from non-target species (mg/kg)	***EU Regulation (EC) No 124/2009*** Food of animal origin from animal species other than chickens for fattening (mg/kg): Egg 0.3, milk 0.005, liver 0.3, kidney 0.1, other food 0.05 New Zealand Egg 0.3

2. Laying hens are identified as the most likely non-target animals to be exposed to unavoidable and unintended carry-over of nicarbazin in non-target animal feed, as feed for chickens and laying hens is often prepared at the same feed mill. Survey or residue monitoring data on nicarbazin in poultry eggs **(Table 2)** and feeding studies on laying hens **(Table 4)** provide evidence for the detectable nicarbazin levels in eggs from laying hens fed feed produced in accordance with good manufacturing practices. **Attachment 1** summarizes the residue data for nicarbazin measured in edible tissues from poultry fed nicarbazin-containing medicated feed.

3. A wide range of nicarbazin levels in eggs with the highest DNC level of 900 µg/kg **(Table 2)** were reported in surveys/residue monitoring of egg samples. As listed in **Table 4**, feeding studies on laying hens resulted in nicarbazin levels in eggs ranging from 226 to 15300 µg/kg. The variation may be explained in part due to the differences in the authorized use-patterns for nicarbazin in broiler chickens. Feeding the broiler chickens with diet containing nicarbazin (in the form of nicarbazin or co-formulated with other ionophores) resulted in liver residue concentrations ranging from around 20-39770 µg/kg, in kidney of 230-5400 µg/kg, in muscle 2-6560 µg/kg, and skin/fat of <10-7750 µg/kg depending on the different feeding levels, WHPs and analytical methodologies **(Attachment 1)**. The highest levels of nicarbazin were measured in eggs and poultry liver compared to the other edible poultry tissues.

4. In terms of possible sources of nicarbazin residues in edible commodities of chicken, carry-over of nicarbazin to non-target animal feed during feed manufacturing (Cannavan et al., 2000; Cannavan and Kennedy, 2000; McEvoy et al., 2003) has been identified as a source of nicarbazin residues in egg. Several authors have also highlighted the ingestion of the droppings containing the excreted (non-absorbed) nicarbazin as a possible cause of nicarbazin residues in broiler chicken tissues (Cannavan and Kennedy, 2000; Kan et al., 1996). They have shown that residue levels in the liver but not in the muscle could exceed the concentration of 200 µg/kg in field conditions following the use of 125 mg nicarbazin/kg feed.

Table 2: Survey or residue monitoring data on nicarbazin in poultry egg[4]

Country	Year	Commodity	LOQ (mg/kg)	MRL (mg/kg)	No. of samples tested	Positive sample n>LOQ (n>LOD)	Residue levels (µg/kg)	Highest residue level (µg/kg)	Reference
Australia	2011-2021	egg	0.01	0.3	301	13 (28)	<10-66	66	Australia NRS data
Belgium	2005	egg			320	13		10	Mortier et al., 2005
Belgium	a) 2002-03 b) 2005	a) egg b) Poultry, egg, rabbit	a) b)	a) b)	a) b) 6	a) b)	a) 3-197 (4), > 10 (2) b)> 10	a) b)	Mortier et al., 2005
Croatia	2009-2011	poultry egg	0.00015 0.015	0.0005 0.05	a) 307 b) 275		a) 1.85 b) 21.1	a) 122.8 b) 314.4	Bilandžić et al., 2013
EU	2004 - 2005	egg	0.001-0.1		3314	23			EFSA 2008
Ireland	2002-2004	poultry egg			546	9	14-122	122	Danaher et al., 2008
North Ireland	1996-1997	egg (190)		0.001	190	39	4-342	342	Cannavan and Kennedy 2000
Italy	a) 2012 b) 2013 c) 2014 d) 2016 e) 2017	a) Poultry, ovine, eggs b) Poultry, eggs c) Poultry, eggs d) Poultry, eggs e) Poultry, eggs	0.001 LOQ		a) 49 (28, 1, 20) b) 49 (31, 18) c) 80 (33, 47) d) 58 (34, 24) e) 46 (34, 12)	a) 4 b) 9 c) 14 d) 20 d) 13	a) 1.4-96 b) 12-21 c) 13-238 d) 13-516 e) 1-321	a) 96 b) 21 c) 238 d) 516 e) 321	Roila et al., 2019
UK	1995-2004	chicken egg			2178	123	> 10 DNC	900	UK-VMD, 1995-2004 EFSA 2018
UK	2007	egg		0.025	234	2	40, 60	60	UK, 2007

[4] Nicarbazin is authorized in the EU and Australia for use in broiler chickens but not approved for laying hens. Residues in eggs are assumed to be from carry-over.

Nicarbazin presence in eggs due to unavoidable and unintended nicarbazin carry-over in animal feed

Step 1. Animal dietary exposure assessment

Option 1

5. A maximum approved rate of 125 mg/kg in broiler feed is considered for proposing action levels in eggs from laying hens utilizing hypothetical carry-over rates. Carry-over of nicarbazin in laying hen feed at a hypothetical level of 1% of the maximum authorized level of 125 mg/kg for broiler chicken would result in carry-over levels of nicarbazin in laying hens feed of 1.25 mg/kg.

Option 2

6. Table 3 summarizes the carry-over levels of nicarbazin in non-medicated animal feed during medicated feed manufacturing. The controlled feed mill studies of Martinez et al. (2018) demonstrated that following medicated feed manufacture at 125 mg/kg nicarbazin and subsequent cleaning and flushing procedures (representing good manufacturing practices), carry-over levels up to 2.2 mg/kg were found in non-medicated feed. This study compared various flushing procedures that reduced the carry-over levels in non-medicated feed. They further claimed that due to the nicarbazin's high electrostatic potential, it tends to cling to the bin walls where the product moisture and environmental conditions may also play roles in its adhesion to the bin walls.

Table 3: Carry-over levels of nicarbazin in non-medicated animal feed during medicated feed manufacturing

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

7. Another study (McEvoy et al., 2003) showed that feed batches produced after the intentional incorporation of nicarbazin into feed result in carry-over levels as high as 8.49 mg/kg in the subsequent feed. A study of German feed-production plants (n≈450) showed less than 4% carry-over levels in more than half of the examined production plants (W. Strauch, 2002 from EFSA, 2008). Another survey of Belgian compound-feed production companies reported the same level of carry-over in pelleted feeds, whereas the mash feeds showed a carry-over level of less than 5% (EFSA, 2008). Studies on carry-over in feed conducted in Italy in 2015 and 2017 reported 0.1-0.8 mg/kg of nicarbazin in poultry non-medicated feed (Roila et al., 2019). In 2006, the Czech Republic reported 43.5 mg/kg of nicarbazin in one sample of non-medicated pre-mixture for pigs out of 254 samples of different feed commodities (EFSA, 2008). Data for nicarbazin residues from a 2010-2012 Italian survey of non-medicated feedstuff showed a highest carry-over level of 0.46 mg/kg (Moretti et al., 2013), whereas another survey conducted in feedstuffs from feed mills or animal farms in Italy from 2010-2017 showed nicarbazin residues as high as 1.46 mg/kg (Annunziata et al., 2018). Nicarbazin is authorized in the EU and Australia for use in broiler chickens but not approved for laying hens, so it is assumed residues in eggs are due to carry-over.

8. "The CGMP regulations require medicated feed manufacturers to use one or more of the approved cleanout procedures, such as cleaning, sequencing, and/or flushing to prevent unsafe contamination by drug carryover (Food and Drug Administration, Department of Health and Human Services, 1976). The most effective cleanout procedure is considered the thorough cleaning of the feed manufacturing equipment. However, given its time-consuming nature and the downtime needed to clean the equipment, sequencing and flushing thoroughly are the most commonly used in the feed industry." […] "When it comes to flushing, the FDA recommends using 50–100 g/kg of the mixer's total capacity as the flush material." (Martinez et al., 2018).

9. Based on the controlled feed mill study of Martinez et al., 2018, under practical conditions (following cleaning and flushing representing GMP), a maximum nicarbazin level of 2.2 mg/kg would be expected in non-medicated feedstuff due to the unavoidable and unintended carry-over of nicarbazin in non-target animal feed.

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

a) Calculating TF for egg

10. As given in **Table 4**, feeding studies with laying hens were used to assess the potential for residues to transfer from feed to egg. DNC is contained predominantly in egg yolk, whereas the HDP is found mainly in albumin (Cannavan et al., 2000, Mortier et al., 2005). DNC is the marker residue for nicarbazin. In whole egg residues were 226 µg/kg on feeding at 1 mg/kg (Oishi and Oda, 1989), 7.69 µg/kg at 0.2 mg/kg, 17.96 µg/kg at 0.4 mg/kg, 64.10 µg/kg at 1.3 mg/kg, 192.3 µg/kg at 3.8 mg/kg and 631 µg/kg at 12.1 mg/kg (Cannavan et al., 2000), 300 µg/kg at 2 mg/kg and 6500 µg/kg at 40 mg/kg (Mortier et al., 2005), 10000 µg/kg at 200 mg/kg (Nose et al 1982) and 15300 µg/kg at 147 mg/kg (Johnston et al., 2001).

11. From **Table 4**, feeding studies with laying hens only fed nicarbazin at levels close to the carry-over level of 2.2 mg/kg were used to assess the potential for veterinary drug carry-over to transfer from feed to egg (Cannavan et al., 2000 and Mortier et al., 2005). As summarized in **Table 4**, TFs for eggs are 0.051 and 0.150, so the median TF is **0.10** (the Nose et al., 1982 study was not used as issues were observed with animal health and the Oishi and Oda et al., 1989 study was excluded as it is unknown if the nicarbazin values are measured as DNC).

Table 4: Compilation of feeding studies of nicarbazin on laying poultry

Species	Feed level (mg/kg)	Duration (days)	LOD (mg/kg)	LOQ (mg/kg)	Residue monitored	Residue level in eggs (µg/kg)	TF_{egg}	Reference
Laying hens*	2 40	14	NS	0.001 CCα 0.012 CCβ	DNC	300 6500	0.150 0.162	Mortier et al., 2005
Laying hens	200	14	NS	NS	DNC	10000	0.05[C]	Nose et al 1982
Laying hens	1.0 0.5 0.1 0.05	10	0.010	NS	DNC	226 - - -	0.226	Oishi and Oda, 1989
Laying hens*	0.2 0.4 1.3 3.8 12.1	16	0.0003	0.001	DNC	7.69 17.96 64.10 192.3 631	0.038[D] 0.045[D] 0.050[D] 0.051[D] 0.052	Cannavan et al., 2000
Laying hens	34.9 54.2 92.5 147	14	0.035[A]	0.117[B]	DNC	4300 9400 13900 15300	0.123 0.173 0.150 0.104	Johnston et al., 2001

*Feeding studies used to calculate TFs.

NS – Not Specified.

[A] LOD = 3 × S/N (Primus et al., 2003)

[B] LOQ = 10 × S/N

[C] laying ceased after 7 days of dosing and restarted after 12 days on non-medicated feed.

[D] TFs were calculated by applying "Y = 0.0195 x + 0.05 equation" derived by Mortier et al., 2005

b) Calculating the anticipated veterinary drug carry-over level in egg

Option 1

12. Considering the carry-over of nicarbazin in laying hen feed at 1% and assuming a median transfer factor of 0.10, the expected nicarbazin residue level in the egg at 1% carry-over would be 125 µg/kg (TF_{egg} × residue level in the feed = 0.10 x 125 mg/kg feed x 1%).

13. Cannavan et al. (2000) showed a linear relationship between nicarbazin feed intake and DNC levels in eggs that could be described by the equation below. They further demonstrated that nicarbazin levels in feed above 2 mg/kg result in DNC levels in eggs greater than the UK differential action limit (DAL) of 100 µg/kg.

Feed-nicarbazin (mg/kg) = 0.0195 × whole egg residue DNC (µg/kg) + 0.05

so

whole egg residue DNC (µg/kg) = (feed nicarbazin (mg/kg) – 0.05)/0.0195

14. From the above equation, DNC residues in eggs of 61.5 µg/kg would be anticipated at feed carry-over of 1% of the maximum authorized level of 125 mg/kg.

Option 2

15. Based on feed mill studies under practical conditions, the maximum nicarbazin carry-over in non-medicated feed is 2.2 mg/kg (Martinez et al., 2018). Utilizing this level, the expected nicarbazin residue level in the egg would be 220 µg/kg (TF_{egg} × residue level in the feed = 0.10 × 2.2 mg/kg feed).

Step 3. Action levels

16. Table 5 summarizes the anticipated nicarbazin residue levels in eggs calculated using the median TF and assuming a hypothetical carry-over rate of 1% (Option 1) and at the maximum concentration in the feed from feed mill studies (Option 2). The nicarbazin residue level in egg at the 1% hypothetical carry-over level would be 125 µg/kg (Option 1), and at 2.2 mg/kg of carry-over level in feed, it would be 220 µg/kg **(Option 2)**.

Table 5: Summary of the anticipated residue levels in chicken egg

Commodity	**TF**	**Anticipated residue level (µg/kg)**	
		Option 1	**Option 2**
		1% (1.25 mg/kg feed)	**2.2 mg/kg feed**
Egg	0.10	125	220

17. In the current example, the anticipated nicarbazin residue level of 220 µg/kg was chosen as the appropriate value for human exposure assessment based on the available feed mill data **(Option 2)** over the conservative default carry-over level of 1%.

18. If no data demonstrate the amount of unavoidable and unintentional veterinary drug carry-over in feed occurring after mitigation steps have been performed, then a discussion is needed to determine whether CCRVDF should consider setting action levels.

Step 4. Human dietary exposure assessment

19. Noting that JECFA is the appropriate committee to perform **Step 4** (Human dietary exposure assessment), in this pilot study, dietary exposure to nicarbazin residues in food resulting from unavoidable and unintended nicarbazin carry-over in non-target animal feed was assessed using the JECFA TMDI (Theoretical Maximum Daily Intake) as a conservative approach.

20. The 2022 JECFA established an ADI of 900 µg/kg bw (DNC) based on toxicological effects (JECFA/94/SC). Based on intended use in broilers considered by the 2022 JECFA, incurred DNC residues in chicken muscle, offal, and skin with fat, at 24 hours withdrawal time and 125 mg/kg feed, the highest Global Estimates of Chronic Dietary Exposure (GECDE) for infants and toddlers estimated by the 2022 JECFA was 210 ug/kg bw per day representing 23% of the upper bound of the ADI of 900 µg/kg bw.

21. For the expected carry-over residues in eggs, a dietary exposure assessment was performed using the 220 µg/kg nicarbazin residue level in eggs, food consumption factor of 100 g of egg, and ADI value of 900 µg/kg bw/day **(Table 6).**

22. As a marker residue to total residue (M:T) ratio is unavailable for eggs, the lowest M:T ratio identified by JECFA in the target animal species (kidney – 0.25) has been used to complete the human dietary exposure assessment.

Table 6: Estimation of dietary exposure to nicarbazin (DNC) residues in chicken eggs using JECFA TMDI approach

Commodity	Daily consumption (g)	Anticipated residue level (µg/kg)	M:T	TMDI (mg)
Egg	100	220	0.25	0.088
TMDI as %ADI				0.16%

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 the ADI

23. The dietary exposure estimates for nicarbazin residues in eggs from non-target animals represent 0.16% of the ADI. Therefore, it can be considered that there is no appreciable risk to consumers' health from the consumption of eggs produced from laying hens consuming a feed with a carry-over level of up to 2.2 mg/kg, regardless of other sources of dietary exposure.

24. Alternatively, JECFA can be requested to advise on an estimate of the appropriate M:T ratio for eggs based on the established M:T ratios in the target animal species, applying safety factors as deemed necessary.

25. In this pilot study, an action level of 0.220 mg/kg for nicarbazin in eggs from laying hens as non-target animals is proposed to accommodate the presence of nicarbazin because of unavoidable and unintended nicarbazin carry-over in animal feed (Table 7). This aligns with similar limits established by the EU and New Zealand for nicarbazin in eggs (0.220 mg/kg).

Table 7: Proposed action level for nicarbazin in chicken egg

Commodity	Proposed action level (mg/kg)	[For comparison] Maximum content (mg/kg)
Egg	**0.220**	0.3 (EU) 0.3 (New Zealand)
Marker residue - 4,4'-dinitrocarbanilide (DNC)		

PILOT STUDY B:
ESTIMATING ACTION LEVELS FOR UNAVOIDABLE AND UNINTENTIONAL LASALOCID CARRY-OVER IN CHICKEN EGG

26. Lasalocid sodium (referred to as lasalocid hereafter) is a monocarboxylic polyether ionophore obtained via fermentation of a strain of *Streptomyces*. It is used to control coccidiosis in chickens for fattening, chickens reared for laying, turkeys, and minor avian species (EFSA, 2017). **Table 8** provides a summary of lasalocid details.

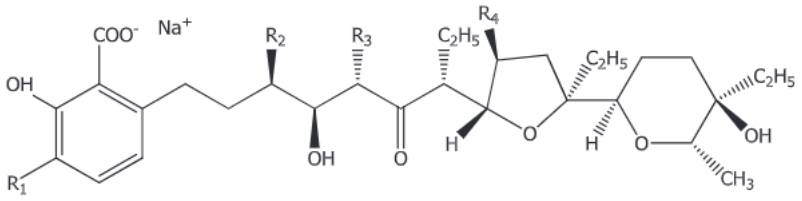
27. Laying hens are identified as the most likely non-target animals to be exposed to unavoidable and unintended carry-over of lasalocid in non-target animal feed, as feed for broiler chickens and laying hens is often prepared at the same feed mill. Survey or residue monitoring data on lasalocid in poultry eggs (**Table 9**) and feeding studies on laying hens (**Table 11**) provide evidence for detectable lasalocid levels in eggs from laying hens fed feed produced in accordance with good manufacturing practices. **Attachment 2** summarizes the residue data for lasalocid measured in edible tissues from poultry fed lasalocid-containing medicated feed.

28. Lasalocid is classified as the most potent ionophore in terms of causing unavoidable residues in eggs (Olejnik et al., 2014; Anadon and Martinez-Larranaga, 2014). This is attributed to the fact that eggs are a major route of excretion for lasalocid residues in laying hens. Therefore, even low levels of lasalocid in feed, resulting from unintentional and unavoidable carry-over, can result in the accumulation of residues at reasonably high concentrations in eggs (Wong and Roxburgh, 2010; Kennedy et al., 1996; Vandenberge et al., 2012).

29. A wide range of lasalocid levels were reported in surveys/residue monitoring of eggs (<1-3450 µg/kg) (**Table 9**). As listed in **Table 11**, feeding studies on laying hens resulted in lasalocid levels in whole eggs ranging from 6.36 – 12,000 µg/kg. The variation is likely explained by the concentration of lasalocid incorporated into feed to conduct each study, as lasalocid deposition into egg has been shown to have a nearly linear relationship with the concentration in feed (EFSA, 2007).

30. In terms of possible sources of lasalocid residues in edible commodities of chicken, carry-over of lasalocid to non-target animal feed during feed manufacturing has been identified as a source of lasalocid residues in egg (Kennedy et al., 1996; Vandenberge et al., 2012). Even if all preventative measures are followed, such as the use of rinsing batching, cross-contamination of residues is unavoidable under practical conditions (EFSA, 2007). Additionally, lasalocid is a very dusty compound, which can easily contaminate feed during the manufacturing process (Rokka et al., 2013).

Table 8: Summary of lasalocid details

Chemical Name	Lasalocid sodium
Marker Residue	Lasalocid A
Structure	 (EFSA, 2017)
Water Solubility (20 ℃)	1,060 mg/L (EFSA, 2017)
log K_{ow}	2.3 (EFSA, 2017)
Target Animal	Chickens for fattening, chickens reared for laying, turkeys for fattening
Authorized maximum content in complete feed and Withholding Period (WHP)	100 mg/kg (broiler chickens and turkeys; Canada) – zero-day (meat) 75-125 mg/kg (broiler chickens and turkeys; US) – zero-day (meat) 75-125 mg/kg (turkeys; UK) – 5-day (meat) 75-100 mg/kg – (broiler chickens and replacement pullets; Australia) – 3-day (meat) and 14-day (egg) 90-125 mg/g – (turkeys; Australia) – zero-day (meat) 75-100 mg/kg – (broiler chickens and replacement pullets; New Zealand) – zero-day (meat) 14-day (egg) 90-125 mg/g – (turkeys; New Zealand) – zero-day (meat)
LOQ	5 µg/kg for all tissues

ADI	0-5 µg/kg bw/day (JECFA/78/SC, 2013)
MRLs for chicken (broilers/layers) (mg/kg)	***AUS*** fat/skin 0.6, kidney 0.7, liver 1.2, muscle 0.4, eggs 0.05 ***Canada*** kidney 0.4, liver 0.4, muscle 0.1, skin/fat 0.4 ***Codex*** muscle 0.4, liver 1.2, kidney 0.6, skin/fat 0.6 ***EU*** muscle 0.06, skin/fat 0.3, liver 0.3, kidney 0.15, eggs 0.15 ***UK VMD*** muscle 0.06, liver 0.3, kidney 0.15, skin/fat 0.3, eggs 0.1 ***US*** skin/fat 1.2, liver 0.4
Maximum content in feed for non-target species (mg/kg)	***EU Regulation EU 574/2011*** Feed materials - 1.25 Compound feed for dogs, calves, rabbits, equine species, dairy animals, laying birds, turkeys (> 16 weeks), and chickens reared for laying (> 16 weeks) – 1.25 Compound feed for chickens for fattening, chickens reared for laying (< 16 weeks), and turkeys (< 16 weeks) for the period before slaughter in which the use of lasalocid sodium is prohibited (withdrawal feed) – 1.25 Other animal species – 3.75
Maximum content in food from non-target species (mg/kg)	***EU Regulation EU 610/2012*** Food of animal origin from animal species other than poultry and bovine: Milk – 0.001 Liver – 0.05 Kidney – 0.02 Other food – 0.005

Table 9: Survey or residue monitoring on lasalocid in poultry egg

Country	Year	Commodity	LOQ (mg/kg)	MRL (mg/kg)	No. of samples tested	Positive sample n>LOQ (n>LOD)	Residue levels (µg/kg)	Highest residue level (µg/kg)	Reference
Australia	2021-22	Whole egg	Limit of Reporting (LOR) – 0.01	0.05	30	1	>LOR to ≤½MRL	NS	NRS, 2021-2022
EU	2005	Egg	CCα = 0.001	MRL NS AL – 0.01 (Belgian Food Agency)	320	24	<1-49	49	Mortier et al., 2005
(Northern) Ireland	1994	Egg	0.001	-	161	107	0.3-129	129	Kennedy et al., 1996; Kennedy et al., 1998
(Northern) Ireland	1995	Egg	0.001	-	220	45 (= 220*0.205)	<1 to >10	NS	Kennedy et al., 1998
Belgium	2004	Egg	-	-	190	-	4-90	90	Mortier et al., 2005
UK	1995-2005	Egg	-	0.01	2855	138	<2-3,450	3450	EFSA, 2007
Italy	2012 2013 2014 2015 2016 2017	Egg	0.001	-	353 animal tissue and egg samples	2 - 1 4 (2) 1 -	1.5-2.0 - 1.2 2.8-1,002 26 -	1,002	Roila et al., 2019
UK	1998 1999 2000 2001 2002 2003 2004 2005 2006 2007	Egg	-	0.002[a] 0.002 0.002 0.002 0.04 0.05 0.05 0.05 0.05 0.15	221 208 212 222 280 275 283 294 249 218	5 21 20 12 18 33 8 4 4 0	<1-3500	3500	Wong and Roxburgh, 2010

NS – Not Specified.
AL – Action Limit.
[a] Defined as action level/maximum residue limit for each specific year.

Lasalocid presence in eggs due to unavoidable and unintended lasalocid carry-over in animal feed

Step 1. Animal dietary exposure assessment

Option 1

31. A maximum approved rate of 125 mg lasalocid/kg in broiler feed is considered for proposing action levels in eggs from laying hens utilizing hypothetical carry-over rates. Carry-over of lasalocid in laying hen feed at a hypothetical level of 1% of the maximum authorized level of 125 mg lasalocid/kg of feed for broiler chickens would result in a carry-over level of lasalocid in laying hen feed of 1.25 mg/kg.

Option 2

32. Table 10 summarizes the carry-over levels of lasalocid in non-medicated animal feed during medicated feed manufacturing, as reported by Kennedy et al. (1996, 1998). In one study (Kennedy et al., 1996), a feed mill prepared a four-ton batch of medicated turkey grower meal using a powdered lasalocid drug premix to provide a final therapeutic concentration of 100 mg lasalocid/kg of feed. The level of lasalocid carry-over was assessed in nine subsequent batches of non-medicated feed. The first batch of non-medicated feed contained 6 mg lasalocid/kg of feed, while the ninth batch of non-medicated feed contained lasalocid concentrations ranging from 0.5-1 mg/kg. In an analogous experiment, cross-contamination of lasalocid from a medicated premix to successive batches of non-medicated premix was measured, with only the first batch of non-medicated premix containing appreciable levels of lasalocid (level not reported) (Kennedy et al., 1996).

33. In a second study conducted by Kennedy et al. (1998), the carry-over of lasalocid into non-medicated feed was evaluated following the manufacturing of medicated feed (100 mg lasalocid/kg of feed) using a granular lasalocid premix. Lasalocid remained present in the first four batches of non-medicated feed but could not be detected in the subsequent five batches. When compared to the results of the study conducted by Kennedy et al. in 1996, the extent of carry-over into non-medicated feed was significantly reduced when medicated feed was manufactured using the granular premix.

34. In both studies described above, there was no indication of any mitigation steps representing good manufacturing practices being performed.

Table 10: Carry-over levels of lasalocid in non-medicated animal feed during medicated feed manufacturing

Level in medicated feed (mg/kg)	Flushing procedure	Level in flush (mg/kg)	Level in non-medicated diet (mg/kg)	Reference
100	-	-	Batch one – 6 Batch nine – 0.5-1	Kennedy et al., 1996
100	-	-	Batch 1 – 3.2 Batch 4 – 0.25	Kennedy et al., 1998

35. A study of German feed-production plants (n≈450) showed less than 4% carry-over levels in more than half of the examined production plants (W. Strauch, 2002 from EFSA, 2007). Another survey of Belgian compound-feed production companies reported the same level of carry-over in pelleted feeds, whereas the mash feeds showed a carry-over level of less than 5% (EFSA, 2007). Studies on carry-over in feed conducted in Italy from 2012 to 2017 reported lasalocid levels in non-medicated poultry feed between 0.1-5.9 mg/kg (Roila et al., 2019). A Swiss feed plant that produces feed for chickens for fattening and laying hen meal found that one production passage without the addition of lasalocid was not sufficient to reduce the contents of the drug in laying hen meal below 30 µg/kg (Noser et al., 2006).

36. In 2007, following a request from the European Commission, the Panel on Contaminants in the Food Chain was asked to deliver a scientific opinion on cross-contamination of non-target feedingstuffs by lasalocid authorized for use as a feed additive. The Czech Republic analyzed 254 samples from feed materials for non-target animal species in 2006. One positive sample, a complete feeding stuff for pigs, contained 8.41 mg lasalocid/kg feed (EFSA, 2007). Denmark reported the analyses of 111 feed samples for non-target species collected between 2004 and 2007 and found one positive sample containing 0.26 mg lasalocid/kg feed (EFSA, 2007). Information from the Rapid Alert System for Food and Feed (RASFF) between April 2002 and April 2006 showed nine incidences where feed for non-target animal species contained lasalocid. The amounts detected were between 0.003 and 12.07 mg lasalocid/kg feed, with one outlier containing 64.6 mg/kg feed. The outlier is most likely due to accidental contamination (EFSA, 2007).

37. Based on the feed mill study of Kennedy et al., 1998, a maximum lasalocid level of 3.2 mg/kg may be expected in non-medicated feedstuff. However, whether mitigation steps representing GMP were performed during this study is unclear. Indeed, "the CGMP regulations require medicated feed manufacturers to use one or more of the approved cleanout procedures, such as cleaning, sequencing, and/or flushing to prevent unsafe contamination by drug carryover (Food and Drug Administration, Department of Health and Human Services, 1976). The most effective cleanout procedure is considered the thorough cleaning of the feed manufacturing equipment. However, given its time-consuming nature and the downtime needed to clean the equipment, sequencing and flushing thoroughly are the most commonly used in the feed industry." […] "When it comes to flushing, the FDA recommends using 50–100 g/kg of the mixer's total capacity as the flush material." (Martinez et al., 2018). Consequently, the anticipated exposure level for non-target animals could not be estimated.

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

a) Calculating TF for egg

38. As given in **Table 11**, feeding studies with laying hens were used to assess the potential for residues to transfer from feed to egg. Lasalocid A is the marker residue for lasalocid. For the study performed by Kennedy et al. (1996), residues in whole eggs were calculated using the following equation:

Concentration in eggs (ug/kg) = 63.6 x Concentration in feed (mg of lasalocid/kg of feed)

39. In whole egg, residue concentrations were 6.36 µg/kg on feeding at 0.1 mg/kg, 19.08 µg/kg at 0.3 mg/kg, 31.8 µg/kg at 0.5 mg/kg, 63.6 µg/kg at 1.0 mg/kg, and 318 µg/kg at 5.0 mg/kg (Kennedy et al., 1996), 370 µg/kg at 3.125 mg/kg, 780 µg/kg at 6.25 mg/kg, and 1410 µg/kg at 12.5 mg/kg (Vandenberge et al., 2012), 11000-12000 µg/kg at 125 mg/kg (EMA, 2006) and 2.0 µg/kg at 1 mg/kg (Rokka et al., 2005).

40. As suitable data is not available to establish, with certainty, that unintended and unavoidable carry-over of lasalocid would occur at a level higher than 1% of the maximum authorized dose (125 mg/kg), a default hypothetical carry-over of 1% (1.25 mg/kg) was considered. From **Table 11,** feeding studies with laying hens only fed lasalocid at levels close to the carry-over level of 1.25 mg/kg were used to assess the potential for veterinary drug carry-over to transfer from feed to egg (Kennedy et al., 1996 and Vandenberge et al., 2012).

41. As summarized in **Table 11,** the TFs for eggs are 0.0636 and 0.118, resulting in a median TF of 0.0908. The TF determined by Rokka et al. (2005) was excluded as it did not state the concentration of lasalocid in the whole egg but only in the egg yolk. The EMA (2006) study was excluded as the laying hens were fed lasalocid at a therapeutic concentration. Therefore, the TF may be overestimated.

Table 11: Compilation of feeding studies of lasalocid on laying poultry

Species	Feed level (mg/kg)	Duration (days)	LOD (µg/kg)	LOQ (µg/kg)	Residue monitored	Residue levels in eggs (µg/kg)	TF_{egg}	Reference
Laying hens*,[a]	0.1 0.3 0.5 1.0 5.0	16	0.3	1.0	Lasalocid A	6.36 19.08 31.8 63.6 318	0.0636	Kennedy et al., 1996
Laying hens*,[a]	3.125 6.25 12.5	14d + 17d depletion period	-	2	Lasalocid A	370 (d16) 780 (d11) 1410 (d14)	0.118 0.125 0.113	Vandenberge et al., 2012
Laying hens	125	12	0.093	10	Lasalocid A	11000-12000 (whole egg; total residues) 291 (egg white) 32500 (egg yolk)	0.088-0.096	EMA, 2006
Laying hens	1.0	21	CCB – 2.0		Lasalocid A	2.0 (egg yolk)	0.002	Rokka et al., 2005

* The peak residue concentration was used to determine the residue levels in eggs.
[a] Feeding studies used to calculate TFs.
NS – Not Specified.

b) Calculating the anticipated veterinary drug carry-over level in egg

Option 1

42. Considering the carry-over of lasalocid in laying hens feed at 1% and assuming a mean transfer factor of 0.0908, the expected lasalocid residue level in the egg would be 113.5 µg/kg (TF_{egg} x residue level in the feed = 0.0908 x 125 mg/kg feed x 1%).

Option 2

43. The anticipated exposure level for non-target animals could not be estimated based on the feed mill study of Kennedy et al., 1998, as GMP could not be verified.

Step 3. Action levels

44. Table 12 summarizes the anticipated lasalocid residue level in eggs calculated using the median TF and assuming a hypothetical carry-over rate of 1% (Option 1). The lasalocid residue level in the egg at the 1% hypothetical carry-over level would be 113.5 µg/kg **(Option 1)**.

Table 12: Summary of the anticipated residue levels in chicken egg

Commodity	TF	Anticipated residue level (µg/kg)	
		Option 1 1% (1.25 mg/kg feed)	Option 2 -
Egg	0.0908	113.5	-

45. In the current example, an anticipated lasalocid residue level of 113.5 µg/kg, based on a default hypothetical carry-over of 1%, was chosen as the appropriate value for the human exposure assessment (**Option 1**). A default carry-over level of 1% was considered as no data demonstrates the amount of unavoidable and unintentional veterinary drug carry-over in feed after mitigation steps have been performed.

46. ***If no data demonstrate the amount of unavoidable and unintentional veterinary drug carry-over in feed occurring after mitigation steps have been performed, then a discussion is needed to determine whether CCRVDF should consider setting action levels.***

Step 4. Human dietary exposure assessment

47. Noting that JECFA is the appropriate committee to perform **Step 4** (Human Dietary Exposure Assessment), in this pilot study, dietary exposure to lasalocid residues in food resulting from unavoidable and unintended lasalocid carry-over in non-target animal feed was assessed using the JECFA TMDI (Theoretical Maximum Daily Intake) as a conservative approach.

48. The 2013 JECFA established an ADI of 0-5 µg/kg bw for lasalocid based on a NOAEL of 0.5 mg/kg body weight per day based on a toxicity study in rabbits (JECFA/78/SC, 2013). The estimated dietary exposure was calculated as 80 µg/person per day, based on median residues for a 1-day withdrawal in chicken, which represents approximately 27% of the upper bound of the ADI, based on a 60 kg individual (JECFA/78/SC, 2013).

49. "The Global Estimates of Chronic Dietary Exposure (GECDE) for the general population is 1.85 ug/kg bw per day, which represents 37% of the upper bound of the ADI. The GECDE for children is 3.38 ug/kg per day, which represents 67% of the upper bound of the ADI. The GECDE for infants is 2.99 ug/kg bw per day, which represents 60% of the upper bound of the ADI." (FAO/WHO, 2015).

50. For the expected carry-over of residues in eggs, a dietary exposure assessment was performed using the 113.5 µg/kg lasalocid A residue level in eggs, food consumption factor of 100 g of egg, marker residue to total residue (M:T) ratio of 0.38 (EMA, 2006) and ADI value of 5 µg/kg bw/day **(Table 13)**.

Table 13: Estimation of dietary exposure to total lasalocid residues in chicken eggs using JECFA TMDI approach

Commodity	Daily consumption (g)	Anticipated residue level (µg/kg)	M:T	TMDI (mg)
Egg	100	113.5	0.38	0.03
TMDI as % ADI				10 %

Dietary exposure estimate (TMDI) = 0.03 mg ÷ 60 kg person/day

= 0.0005 mg/kg bw/day

= 0.0005 mg/kg bw/day ÷ 0.005 mg/kg bw/day x 100%

= 10 % of the ADI

51. The dietary exposure estimates for lasalocid residues in eggs from non-target animals represent 10% of the ADI. Therefore, it can be considered that there is no appreciable risk to consumers' health from the consumption of eggs produced from laying hens consuming a feed with a carry-over level of up to 1.25 mg lasalocid/kg, regardless of other sources of dietary exposure.

52. In this pilot study, it is proposed to establish an action level of 0.1 mg/kg (rounded down from 0.113 mg/kg) for lasalocid in eggs from laying hens as non-target animals to accommodate the presence of lasalocid because of unavoidable and unintended lasalocid carry-over in animal feed **(Table 14)**.

Table 14: Proposed action level for lasalocid in chicken egg

Commodity	Proposed action level (mg/kg)	[For comparison] Maximum content (mg/kg)
Egg	0.1	0.15 (MRL - EU) 0.05 (MRL - Australia)
Marker residue – Lasalocid A		

ANNEX

National and Regional Guidelines

Canada

1. Medication Sequencing Guideline for Management of Drug Carryover (http://inspection.gc.ca/animals/feeds/inspection-program/medication-sequencing/eng/1389362488069/1389362490053)
2. Validation studies for Modification of Sequencing Guidelines (http://inspection.gc.ca/animals/feeds/inspection-program/sequencing-guidelines/eng/1373325944197/1373325944713)
3. Measurement of Feed Carryover Level (http://inspection.gc.ca/animals/feeds/inspection-program/measurement-of-feed/eng/1373325386112/1373325437132)
4. Medication Residues Validation Testing Procedures for Equipment Cleanout Procedures (http://inspection.gc.ca/animals/feeds/inspection-program/equipment-cleanout/eng/1373325971995/1373325972541)

European Union

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Attachment 1

Table: Compilation of residues data for nicarbazin measured in edible tissues from poultry fed nicarbazin medicated feed

Species	Feed level (mg/kg)	Dosing period (days)	LOD (mg/kg)	LOQ (mg/kg)	WHP (days)	Residue level (mg/kg)				Reference
						Liver	Kidney	Muscle	Skin/Fat	
Chicken	100 (WF or DL)	28	NS	0.001	9	0.2238± 0.0742 (DL) 0.0237±0.0039 (WF)	-	0.0024±0.0003 (WF) 0.014±0.0084 (DL)	-	Cannavan and Kennedy, 2000
Chicken	13.5 (WF or DL)	32	NS	0.001	5	1.157 (DL) 0.992 (WF)	-	0.055 (DL) 0.028 (WF)	-	Cannavan and Kennedy, 2000
Chicken	125	28	NS	0.05 liver 0.1 kidney 0.025 muscle 0.025 skin/fat	1 (24 h)	9.249±1.804	3.007±1.095	2.110±0.506	2.327±0.372	EFSA 2010a
Chicken	125	42	0.03	0.1	1 (24 h)	14.4-21	2.8-5.4	1.4-2.2	1.6-3.0	Wood and Dowling, 1980; JECFA 1999
Chicken	125	49	0.02[A]	0.1[A]	1 (24 h)	2.69-9.12 6.62±1.08	-	0.85-1.23 0.98±0.088	0.66-0.99 0.88±0.042	Kramer, 1990; JECFA 1999; ANADA 200-027
Chicken	50 (+50 lasalocid)	42	NS	NS	1 (24 h)	8.57±1.432	3.51±1.12	1.64±0.294	1.95±0.257	EFSA 2021
*Chicken	50 (+50 monensin)	35	NS	0.1	0.25 (6 h)	8.331 (x+2SD)	1.514 (x+2SD)	1.182 (x+2SD)	1.723 (x+2SD)	EFSA 2017
*Chicken	55 (+55 monensin)	10	NS	NS	0.25 (6 h)	6.857±0.920	0.806±0.584	0.761±0.207	1.269±0.326	EFSA 2017; EFSA 2018b

Species	Feed level (mg/kg)	Dosing period (days)	LOD (mg/kg)	LOQ (mg/kg)	WHP (days)	Residue level (mg/kg)				Reference
						Liver	Kidney	Muscle	Skin/Fat	
*Chicken	45.4 (+45.4 narasin)	63	NS	2	0	7.6	-	<2	<2	NADA 138-952a
*Chicken	50 (+50 narasin)	35	NS	0.05 liver 0.1 kidney 0.025 muscle 0.025 skin/fat	0	9.19±0.956	4.29±1.034	1.61±0.149	2.04±0.479	NADA 138-952b; EFSA 2010b
*Chicken	70 (+70 narasin)	42	NS	0.02	0 (3h)	8.988±1.965	3.525±1.485	1.813±0.43	2.018±0.66	EFSA 2019
*Chicken	45 (+27 narasin + 4 lincomycin)	NS	NS	NS	0 (6h)	8.27±1.75	-	-	-	NADA 140-947
*Chicken	45 (+27 narasin + 50 bacitracin + 45.4 roxarsone)	21	NS	NS	0 (6 h)	10.4 (2.0-16.5)	-	-	-	NADA 141-112; NADA 141-113
*Chicken	50 (+50 narasin + 200 bacitracin	49	0.1	NS	0 (6h)	8.5±2.96	-	-	-	NADA 140-926; NADA 141-124; NADA 141-529
*Chicken	113 (+20 bambermycins, +50 roxarsone	48	NS	1	0	32.9±6.87	-	4.7±1.86	6.2±1.55	NADA 140-339
*Turkey	50 (+50 monensin) Turkeys	112 (16 wk)	0.01	0.1	0.25 (6 h)	0.276 (5 <LOQ, 1<LOD)	<LOQ	<LOD	<LOQ	EFSA 2017
*Turkey	109	112 (16 wk)	NS	1	0 (1 h)	1.22 (x+2SD)	<LOQ	<LOQ	<LOQ	EFSA 2018a
*Feeding studies with practical zero withdrawal times (less than 12 hours).										

Attachment 2

Table: Compilation of residue data for lasalocid measured in edible tissues from poultry fed lasalocid medicated feed.

Species	Feed level (mg/kg)	Dosing period (days)	Marker Residue	LOD (µg/kg)	LOQ (µg/kg)	WHP (days)	Residue level (µg/kg)				Reference
							Liver	Kidney	Muscle	Skin/Fat	
Chicken	125	7	Lasalocid A	20	NS	0 1 3 5 7	290 90 20 40 -	130 30 30 30 -	50 - - - -	340 70 40 40 -	EFSA, 2004
Chicken	90	14	Lasalocid	0.01 (Muscle) 0.09 (Liver)	0.02 (Muscle) 0.15 (Liver)	0 5 7	400 30 20	- - -	10 0.5 0.5	- - -	Kennedy et al., 1995
Chicken	125 then 132	34 then 21	Total Radioactivity	NS	NS	0 1 2 3 4 5	11930 2630 1720 1590 1370 1150	2480 360 230 < 200 < 200 < 200	610 60 30 < 200 < 200 < 200	1590, 860 220, 140 130, 60 < 200 < 200 < 200	EMA, 2004
Chicken	75 (+50 roxarsone)	56	lasalocid	NS	50	0 1 2 3	< LOQ < LOQ < LOQ < LOQ	< LOQ < LOQ < LOQ < LOQ	< LOQ < LOQ < LOQ < LOQ	370 ± 40 50 < LOQ < LOQ	NADA 141-488
Chicken	75 (+50 roxarsone + 2.0 lincomycin)	56	Lasalocid	NS	50	0 1 2 3	< LOQ < LOQ < LOQ < LOQ	< LOQ < LOQ < LOQ < LOQ	< LOQ < LOQ < LOQ < LOQ	360 ± 30 < LOQ < LOQ < LOQ	NADA 141-488
Chicken	125 (+2.2 lincomycin + 50 roxarsone)	56	Lasalocid	NS	50	0 1 2 3 4	- - - - -	- - - - -	- - - - -	270 ± 110 70 ± 20 < LOQ < LOQ < LOQ	NADA 141-488
Chicken	125 (+55 bacitracin zinc)	42	Lasalocid	NS	15	0				428 ± 127	NADA 107-996
Turkey	125	14	Total Radioactivity	20	NS	0.33 1 2 3 4 5	3380 ± 570 1430 1490 1040 1100 870	430 ± 50 200 170 120 120 80	300 ± 10 < LOD < LOD < LOD < LOD < LOD	300 ± 110 160 110 100 140 90	NADA 096-298
Turkey	125 (+55 bacitracin zinc)	105	Lasalocid	NS	5	0.25	37.3 ± 30.4	-	-	-	NADA 141-109
Quail	90	27	Lasalocid A	NS	NS	0 3 6 9	- - - -	- - - -	- - - -	298.3 55 30.8 33.7	EMA, 2004
Pheasant	132	7	Lasalocid A	NS	NS	0	28.5	-	-	30.7	EMA, 2004
NS – Not Specified.											

APPENDIX III

PROPOSAL TO DEVELOP CARRY-OVER RISK MANAGEMENT INFORMATION AND A RISK MANAGEMENT DECISION TOOL

ALTERNATIVE PROPOSAL FROM THE UNITED STATES OF AMERICA (USA)

(For comments)

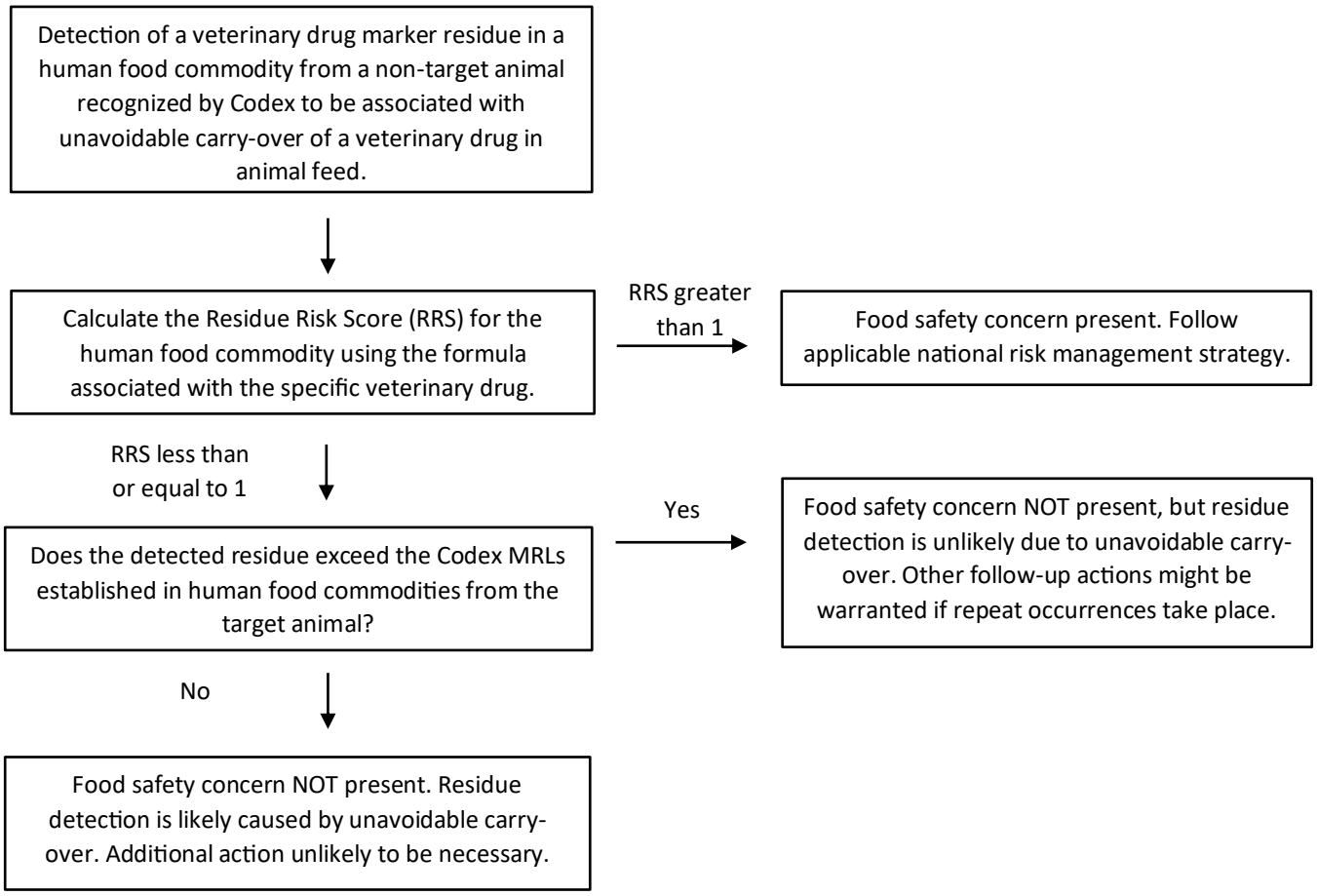
Introduction

1. To circumvent the challenge of data availability, the United States proposes that the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) develop carry-over risk management information on a case-by-case basis and a Risk Management Decision Tool (RMDT). Unlike action levels, this approach does not require estimates of the carry-over amount and the associated residue concentrations in the food commodity. Also, this approach avoids potentially establishing a residue level that is incompatible with residue amounts detected in human food commodities caused by unavoidable carry-over in animal feed. Instead, this approach provides a tool that competent authorities can choose to employ when they detect a veterinary drug residue in a human food commodity from a non-target animal recognized by Codex to be associated with unavoidable carry-over of a veterinary drug in animal feed.

2. The proposed RMDT is outlined below, followed by descriptions of how the proposed Residue Risk Score (RRS) is calculated, the role of CCRVDF, and how CCRVDF can communicate this information. Following these descriptions, an example is provided using nicarbazin in eggs from laying hens.

Proposed Risk Management Decision Tool (RMDT)

Risk Management Decision Tool (RMDT) for Residues of Veterinary Drugs in Foods Associated with Unavoidable Carry-over in Animal Feed



3. The RMDT is a decision tree that enables competent authorities to evaluate the human food safety risk associated with detecting the veterinary drug residue in the human food commodity from the non-target animal when unavoidable carry-over of the veterinary drug in the animal feed is the suspected cause. The competent authority can then make a risk management decision based on the specific residue level that is detected and the associated human food safety risk.

4. In general, the RMDT calls for the calculation of a Residue Risk Score (RRS) that places the detected residue value into the context of the established health-based guidance value (HBGV) for the veterinary drug. An RRS less than or equal to one indicates that the detected residue is not a food safety concern. An RRS greater than one indicates that the detected residue represents a food safety concern. As explained in later detail, the RRS equation will be unique for a specific veterinary drug and human food commodity determined by CCRVDF to be affected by unavoidable carry-over. The specific RRS equation will be developed by CCRVDF, as explained later, and can be communicated in the *Maximum Residue Limits and Risk Management Recommendations for Residues of Veterinary Drugs in Foods* (CXM 2).

5. When the RRS is less than or equal to one, indicating no food safety concern, the decision tree then asks whether the detected residue exceeds the Codex MRLs established for the target animal. The answer to this question informs the risk manager whether the detected residue is likely caused by unavoidable carry-over. If the detected residue exceeds the Codex MRLs established for the target animal, then it is unlikely to be caused by unavoidable carry-over because the Codex MRLs for the target animal are based on a pharmacological dose of the veterinary drug, and true unavoidable carry-over amounts are likely to be much lower than a pharmacological dose. Likewise, if the detected residue is less than the Codex MRLs for the target animal, unavoidable carry-over is likely the cause. This information enables the risk manager to determine if additional follow-up actions are necessary.

Calculation of the Residue Risk Score

6. The Residue Risk Score (RRS) is a metric used to determine whether there is a food safety concern associated with veterinary drug residues in human food commodities caused by unavoidable carry-over of veterinary drugs in animal feed. The RRS value quantifies the human food safety risk in relation to the established Codex HBGV for the veterinary drug. The general calculation is as follows:

- RRS = (Detected Marker Residue Concentration (µg/kg) × Risk Score Correction Factor) + GVP Risk Score
- Where…
- Risk Score Correction Factor = a numerical value that converts the detected marker residue concentration to a risk score value
- GVP Risk Score = Fraction of the HBGV utilized when the drug is used in accordance with Good veterinary Practices (GVPs)

7. The information needed to calculate the RRS (*i.e.,* Risk Score Correction Factor and GVP Risk Score) will be established by CCRVDF on a case-by-case basis for a specific veterinary drug and human food commodity determined by CCRVDF to be affected by carry-over. After the RRS is developed, CCRVDF can communicate it within CXM 2. In doing so, the competent authority only needs to apply the RRS equation to the detected residue value.

Determination of the Risk Score Correction Factor and GVP Risk Score

8. For a specific veterinary drug and human food commodity, CCRVDF will determine the following:

8.1 Risk Score Correction Factor: The risk score correction factor is a numerical value that enables rapid conversion of the detected marker residue concentration in the human food commodity to a risk score value. It converts the measured marker residue value into a number that quantifies the risk of the detected residue in relation to the Codex HBGV. Essentially, this risk score value is the percentage of the Codex HBGV that would be utilized by the detected residue, expressed as decimal. Similar to and building upon Step 4 in the Action Level discussion paper, the risk score correction factor is based on the Theoretical Maximum Daily Intake (TMDI) model and consolidates the mathematical steps for the TMDI calculation into a single step for the affected commodity. The risk score correction factor is derived from the following:

8.1.1. TMDI consumption factor for the commodity (*i.e.* 0.3 kg muscle, 0.1 kg liver, 0.05 kg kidney, 0.05 kg fat (skin/fat), 1.5 kg milk, 0.1 kg eggs, 0.02 kg honey)

8.1.2 TMDI human body weight (60 kg)

8.1.3 Health-Based Guidance Value (*e.g.*, ADI or ARfD)

8.1.4 An estimated marker residue to total residue ratio (M:T) determined by CCRVDF.

8.1.4.1 The estimated M:T ratio will be based on the JECFA-derived M:T ratios associated with the veterinary drug in the target animal, applying uncertainty factors as deemed necessary if an experimentally derived M:T ratio is not available for the affected commodity.

9. The calculation is as follows:

$$\text{Risk Score Correction Factor} = \frac{\left(\frac{\text{TMDI consumption value (kg)}}{\text{estimated M:T}}\right)}{(\text{HBGV (µg/kg)} \times \text{60 kg body weight})}$$

8.2 GVP Risk Score: CCRVDF will identify the GVP Risk Score based on the JECFA evaluation which recommended the Codex MRLs in the target animal. The GVP Risk Score is the percentage of the HBGV utilized when the veterinary drug is used in accordance with GVPs expressed as a decimal. For example, if JECFA determined that use of the veterinary drug in accordance with GVPs results in 23% of the ADI being utilized, then the GVP Risk Score is equal to 0.23.

Communication of the Residue Risk Score Calculation and Risk Management Decision Tool

10. CCRVDF can communicate the information needed to calculate the RRS within CXM 2 for each specific veterinary drug residue and human food commodity determined to be affected by unavoidable carry-over. This could be done by providing text describing the issue and the RRS equation to be applied to the detected marker residue concentration in the affected human food commodity.

11. The Codex Committee on Contaminants in Foods (CCCF) has a similar decision tool for contaminants in food where there is no regulatory level, and CCCF has communicated this according to the *Guidelines for Rapid Risk Analysis Following Instances of Detection of Contaminants in Food where there is No Regulatory Level* (CXG 92-2019)[1]. Similarly, CCRVDF could communicate the general information on the RMDT as a Codex Guideline. The Codex Guideline would refer to the *Maximum Residue Limits and Risk Management Recommendations for Residues of Veterinary Drugs in Foods* (CXM 2)[2] for the information needed to calculate the RRS for each specific veterinary drug residue and human food commodity determined to be affected by unavoidable carry-over.

12. Below is an outline of how this proposed process might work, using nicarbazin in eggs as an example.

Nicarbazin in Eggs Example

Step 1: ***Review of unavoidable carry-over information***

13. CCRVDF would review information on the occurrence of unavoidable carry-over of nicarbazin in laying hen feed and its potential to cause detectable residues in eggs from laying hens.

Step 2: ***Determination of GVP Risk Score and Risk Score Correction Factor***

14. If CCRVDF determines that sufficient information demonstrates that detectable residues in eggs from laying hens is associated with unavoidable carry-over of nicarbazin in laying hen feed, then CCRVDF would determine the appropriate GVP Risk Score and Risk Score Correction Factor.

- **GVP Risk Score:** The 94th meeting of JECFA determined that the maximum estimated ADI utilization is 23% when nicarbazin is used in accordance with GVPs[3]. Therefore, the GVP Risk Score is 0.23.
- **TMDI Consumption Factor for Eggs**: 0.1 kg
- **CCRVDF-estimated M:T for Eggs**: 0.25 (only an example estimate)
- **Nicarbazin HBGV (ADI)**: 900 µg/kg bw

15. Therefore, the Risk Score Correction Factor for nicarbazin in eggs equals 7.41×10^{-6}

$$\text{Risk Score Correction Factor} = \frac{\left(\frac{0.1\ \text{kg}}{0.25}\right)}{(900\ \mu\text{g/kg} \times 60\ \text{kg body weight})} = 7.41 \times 10^{-6}$$

Step 3: ***Communication of risk management information***

16. CCRVDF would communicate the risk management information for nicarbazin in eggs in CXM 2. The language that follows is provided only as an example.

NICARBAZIN (coccidiostat)

17. Codex has adopted Maximum Residue Levels (MRLs) for nicarbazin in chicken muscle, liver, kidney, and skin with adhering fat. Evidence indicates that unavoidable carry-over of nicarbazin can occur in non-target animal feed intended for laying hens despite adherence to Good Veterinary Practices and Good Manufacturing Practices. This can result in residues of nicarbazin in eggs from laying hens. For this reason, competent authorities should ensure that appropriate mitigation steps are taken to reduce the carry-over of nicarbazin into feed intended for laying hens. Appropriate mitigation steps can be found in the Code of Practice on Good Animal Feeding (CXC 54). In cases where the marker residue for nicarbazin (DNC) is detected in eggs from laying hens, competent authorities can apply the procedures outlined in the Risk Management Decision Tool (RMDT). The equation for calculating the Residue Risk Score (RRS) used in the RMDT for the marker residue for nicarbazin in eggs from laying hens is the following.

$$\text{RRS} = \left(\text{Marker Residue Concentration } (\mu\text{g/kg}) \times 7.41 \times 10^{-6}\right) + 0.23$$

1 https://www.fao.org/fao-who-codexalimentarius/committees/committee/related-standards/en/?committee=CCCF

2 https://www.fao.org/fao-who-codexalimentarius/committees/committee/related-standards/en/?committee=CCRVDF

3 Evaluation of certain veterinary drug residues in food. Report of the 94th Meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 1041.

Step 4: ***Hypothetical Implementation of the Residue Risk Score Calculation and Risk Management Decision Tool***

18. Hypothetically, if a competent authority detects the marker residue for nicarbazin (DNC) in eggs at a concentration of 300 µg/kg and employs the RMDT, the competent authority would calculate the RRS to be 0.2322.

$$RRS = \left(300\ \mu g/kg \times 7.41 \times 10^{-6}\right) + 0.23 = 0.2322$$

19. In this hypothetical example, the RMDT would indicate that there is no food safety concern associated with the eggs containing the marker residue for nicarbazin (DNC) at a concentration of 300 µg/kg and that unavoidable carry-over likely is the cause.

APPENDIX IV

LIST OF PARTICIPANTS

Chair Australia Dugald MacLachlan Department of Agriculture, Fisheries and Forestry	Vice-Chair Canada Manisha Mehrotra Health Canada

MEMBER COUNTRY/ORGANIZATION[1]	**OBSERVER**[2]
1. Argentina	1. International Feed Industry Federation (IFIF)
2. Australia	
3. Brazil	
4. Canada	
5. Chile	
6. Costa Rica	
7. Denmark	
8. Egypt	
9. France	
10. Germany	
11. Honduras	
12. Hungary	
13. India	
14. Indonesia	
15. Iran	
16. Italy	
17. Japan	
18. Maroc	
19. Panama	
20. Republic of Korea	
21. Saudi Arabia	
22. Thailand	
23. United Arab Emirates	
24. United States	