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Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 8 **CX/RVDF 23/26/8**

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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 UNINTENDED AND UNAVOIDABLE CARRYOVER OF VETERINARY DRUGS FROM FEED TO FOOD OF ANIMAL ORIGIN

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

Codex members and observers wishing to submit comments the proposed approach (criteria and procedures) as presented in Appendix I-Part I should do so as instructed in CL 2022/77-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 established[3] to prepare a discussion paper on the possible criteria or requirements for developing tolerance levels (action levels) for compounds in edible tissues/commodities due to the unintended and unavoidable carryover of authorized veterinary drugs in feed and their transfer from feed into food of animal origin and to use nicarbazin as a pilot case (Appendix I).

WORK PROCESS: PARTICIPATION AND METHODOLOGY

2. The EWG registered 15 Member countries and one observer to participate in this work. The List of Participants is presented in Appendix II.

3. The EWG Chairs circulated the first draft document to the EWG members on 5th April 2022 in English. In line with the terms of reference (TOR) of the EWG, the document contained proposed criteria for establishing action levels, a proposed procedure as well as a pilot study estimating action levels for unavoidable and unintentional nicarbazin carry-over in chicken eggs. Four EWG members and one observer organisation provided comments on this draft.

4. On the basis of these comments, the EWG Chairs prepared a second draft document and circulated it to the EWG members on the 18th August 2022. Three EWG members and one observer organisation sent their comments on this draft.

5. The EWG Chairs finalized the discussion paper and submitted it to the Codex Secretariat for consideration by Codex members and observers.

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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 REP21/RVDF25, para. 139

SUMMARY OF DISCUSSION

6. In their comments, there were two main areas of divergent views. The inclusion of an option to use default levels of carry-over from medicated to unmedicated feed was not agreed. 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. Lastly, 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. The additional contribution of carry-over to residues in edible commodities is low with some members suggesting 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.

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

RECOMMENDATIONS

9. Codex members and observers are invited to consider:

   i. the proposed approach for the establishment of action levels as presented in the discussion paper Appendix I, Part I for comments and consideration by CCRVDF26.

   ii. a pilot study using nicarbazin residues in chicken eggs, as presented in the discussion paper, which illustrates the proposed approach for estimating action levels as presented in Appendix I, Part II for information to support comments on the proposed approach.

APPENDIX I

DISCUSSION PAPER ON 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

INTRODUCTION

1. The Codex Committee on Residues of Veterinary Drugs at its 25th Session (CCRVDF25, 2021) agreed to explore the possibility of setting action levels for the unavoidable and unintended presence of residues of veterinary drugs in food commodities resulting from carry-over of veterinary drugs in feed.[4]
2. CCRVDF25 agreed to establish an electronic Working Group, chaired by Australia and co-chaired by Canada to;
   - prepare a discussion paper on criteria or requirements for elaborating action levels for food from non-target animals to accommodate unavoidable and unintended veterinary drug from feed carry-over.
   - conduct a pilot study on the establishment of action levels for nicarbazin in food products from non-target animal (e.g., action levels for nicarbazin in chicken eggs) resulting from unavoidable and unintentional nicarbazin carry-over in non-target feedingstuffs.
3. The discussion paper is to be presented to the 26th Session of the CCRVDF.

SCOPE

Develop a discussion paper on criteria or requirements for the establishment of action levels for residues of veterinary drugs in food of animal origin resulting from unintended and unavoidable veterinary drug carry-over from feed into a non-target animal by considering the existing policies, guidelines, codes of practice and standards/tolerance levels established by national and international regulatory bodies, and the scientific literature.

DEFINITIONS AND TERMS USED IN THIS DOCUMENT

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

Acceptable daily intake (ADI): The estimate of the amount of a chemical in food or drinking-water, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk to the consumer (EHC 240: Principles for Risk Assessment of Chemicals in Food 2009).

Acute reference dose (ARfD): The estimate of the amount of a substance in food or drinking water, expressed on a body weight basis, that can be ingested in a period of 24 h or less without appreciable health risk to the consumer (EHC 240: Principles for Risk Assessment of Chemicals in Food 2009).

Dietary exposure assessment: The qualitative and/or quantitative evaluation of the likely intake of chemicals (including nutrients) via food, beverages, drinking-water, and food supplements. Synonymous with: Intake assessment (EHC 240: Principles for Risk Assessment of Chemicals in Food 2009).

Feed (Feedingstuff): Any single or multiple materials, whether processed, semi-processed or raw, which is intended to be fed directly to food-producing animals (FAO, WHO, 2008).

Good Practice in the Use of Veterinary Drugs: The official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions (Codex Alimentarius Commission: Procedural Manual 19th ed. 2010).

Health-based guidance value (HBGV): A numerical value derived by dividing a point of departure (a no-observed-adverse-effect level, benchmark dose or benchmark dose lower confidence limit) by a composite uncertainty factor to determine a level that can be ingested over a defined time period (e.g., lifetime or 24 h) without appreciable health risk (EHC 240: Principles for Risk Assessment of Chemicals in Food 2009).

[4] REP17/RVDF23 paras. 75-88 and CX/RVDF 16/23/7. Available for downloading at: https://www.fao.org/fao-who-codexalimentarius/meetings/detail/en/?meeting=CCRVDF&session=23

Limit of Detection (LOD): The minimum concentration of a component in a dietary sample that can be qualitatively detected, but cannot be quantitatively determined, under a pre-established set of analytical conditions. (EHC 240: Principles for Risk Assessment of Chemicals in Food 2009)

Limit of Quantification (LOQ): The minimum concentration of a component that can be determined quantitatively with acceptable accuracy and consistency. It often approximates to a value of 3 times the limit of detection (EHC 240: Principles for Risk Assessment of Chemicals in Food 2009).

Codex Maximum Residue Limit (MRL) for veterinary drug: The maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food (Codex Alimentarius Commission: Procedural Manual 19th ed. 2010).

Marker Residue (veterinary drugs) (MR): The parent drug, or any of its metabolites, or a combination of any of these, with a known relationship to the concentration of the total residue of toxicological concern or microbiological concern in each of the various edible tissues at any time between administration of the drug and the depletion of residues to safe levels. (EHC 240: Principles for Risk Assessment of Chemicals in Food 2009).

MR:TR: Ratio between marker residue (MR) and total residue (TR) of toxicological concern or microbiological concern.

Medicated feed: Any mixture of a veterinary drug or drugs and feed or feeds that is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties as a medicinal product (FAO, WHO, 2008).

Non-medicated feed: Feed (feedingstuff) that does not intentionally contain veterinary drug or drugs.

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

Residues of veterinary drugs: The parent compounds and/or their metabolites in any edible portion of the animal product. They include residues of associated impurities of the veterinary drug concerned (EHC 240: Principles for Risk Assessment of Chemicals in Food 2009).

Risk assessment: A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment and (iv) risk characterization (FAO, WHO, 2018a).

Sequencing: A pre-planned order of production of medicated feed designed to control veterinary drug carry-over into subsequent batches of feed for target or non-target animal.

Target-class of animal: An animal, including its production class, for which a veterinary drug is approved for use in, and to which that drug is intentionally administered.

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

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

Veterinary drug: Any substance applied or administered to any food producing animal, such as meat or milk producing animals, poultry, fish, or bees, whether used for therapeutic, prophylactic, or diagnostic purposes or for modification of physiological functions or behaviour (EHC 240: Principles for Risk Assessment of Chemicals in Food 2009).

Withholding Period (WHP, also called Withdrawal period): The period of time between the last administration of a drug and the collection of edible tissue or products from a treated animal that ensures the contents of residues in food comply with the maximum residue limit for this veterinary drug (CAC/MISC 5-1993).

PART I:

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

(For comments)

Proposal

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

Q1. What methodology should be used by CCRVDF when setting action levels to accommodate presence of residues due to unavoidable and unintended veterinary drug carry-over in non-target animal feed?

Q2. What are the considerations that should be used to determine an acceptable maximum level of unavoidable and unintended veterinary drug carry-over in non-target animal feed?

General criteria on the proposed approach

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

Q3. Are the proposed criteria suitable?

Proposed procedure

1. The following four steps are proposed 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 (CXG 80-2013) and risk assessment approaches.

   Step 1. Animal dietary exposure assessment

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

   Step 3. Action levels

   Step 4. Human dietary exposure assessment

2. It is proposed that the Codex Committee on Residues of Veterinary Drugs (CCRVDF) perform **Step 1** (Animal dietary exposure assessment), **Step 2** (Estimates of anticipated residue levels in food commodities of animal origin) and **Step 3** (Action levels). Then, under **Step 4**, CCVRDF to requests JECFA to conduct an appropriate exposure assessment based on the proposed action level derived under **Step 3**. An electronic working group (EWG) within CCRVDF is proposed to perform **Steps 1** through **3**.

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

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

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

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

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

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

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

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

Step 1: Animal dietary exposure assessment

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

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

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

Option 2 –The expected concentration of unavoidable and unintended veterinary drug carry-over in non-medicated feed determined by feed mills operating under routine good manufacturing conditions (e.g., maximum observed concentration, median, or 95th percentile concentration of detected veterinary drug carry-over in surveys of feed or reported by feed mills).

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

a) Calculating the Transfer Factors (TFs)

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

TF can be calculated as follows:

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

Notes:

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

b) Calculating the anticipated veterinary drug transfer level

Anticipated veterinary drug transfer levels in edible animal commodities (including muscle, liver, kidney, skin/fat, milk or egg) of non-target animals can be calculated using the TFs and the level of veterinary drug in the animal's feed estimated either by **(Option 1)** hypothetical carry-over rates of the highest authorised dose of the veterinary drug in feed for the target-class of animals or **(Option 2)** the maximum observed level or 95th percentile carry-over level as measured in non-medicated feed from feed mill studies operating under routine good manufacturing conditions.

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

Step 3: Action levels

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

Notes:

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

1. the concentration estimated by using the TF, or
2. the residue concentration determined to be caused by unavoidable and unintended veterinary drug carry-over in animal feed that satisfied bullet point #2 of the General Criteria.

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

Step: 4 Human dietary exposure assessment

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

Notes:

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

Additional questions

The following questions still need consideration by CCRVDF26:

Q4. Which approach should be used to estimate the veterinary drug carry-over level in non-target animal feed for non-target animal (e.g., hypothetical carry-over rates, highest residue levels in feed from feed mills, etc.)?

Q5. What assumptions should be made in calculating TFs?

Q6. What level of importance should be given to monitoring data when relevant monitoring data is available?

Q7. What approach should be given to determining an appropriate MR:TR (Marker Residue: Total Residue of toxicological concern or microbiological concern) ratio when there is no specific radiolabelled data for a food commodity exposure via veterinary drug carry over?

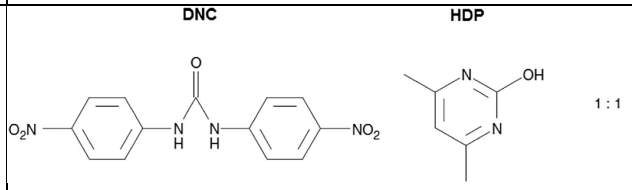
Q8. Are there other considerations that have not been considered in this risk assessment procedure?

Q9. Are the proposed roles and responsibilities appropriate in establishing action levels?

PART II
PILOT STUDY
ESTIMATING ACTION LEVELS FOR UNAVOIDABLE AND UNINTENTIONAL NICARBAZIN CARRY-OVER IN CHICKEN EGG
(For information)

1. Nicarbazin is a non-ionophoric coccidiostat that is administered in feed to broiler chickens for the prevention and control of 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,N1- bis(4-nitropheneyl urea) and 1,3-N,N1-bis(4-nitropheneyl urea). 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. **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	 (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
Authorised 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 residues 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 authorised 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 in comparison 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 use of 125 mg nicarbazin/kg feed.

Table 2: Survey or residue monitoring data on nicarbazin in poultry egg[5]

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

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

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

Step 1. Animal dietary exposure assessment

Option 1

A maximum approved rate of 125 mg/kg in the 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 hypothetical levels of 1%, 2.5%, 3% and 5% of the maximum authorised level of 125 mg/kg for broiler chicken would result in carry-over levels of nicarbazin levels in laying hens feed of 1.25, 3.125, 3.75 and 6.25 mg/kg respectively.

Option 2

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 has a tendency 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

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 carry-over levels of less than 4% 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 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 authorised in the EU and Australia for use in broiler chickens, but not approved for laying hens, so it is assumed residues in egg are due to carry-over.

"The CGMP regulations require medicated feed manufacturers to use one or more of the approved cleanout procedure, 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 down time needed to thoroughly clean the equipment, sequencing and flushing 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).

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 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

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).

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 summarised in **Table 4**, TFs for egg 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, 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

Considering carry-over of nicarbazin in laying hens feed at 1, 2.5, 3 and 5% and assuming a median transfer factor of **0.10**, the expected nicarbazin residue levels in egg at 1, 2.5, 3 and 5% carry-over would be 125 µg/kg (TF_{egg} × residue level in the feed = 0.10 x 125 mg/kg feed x 1%), 312.5 µg/kg (0.10 x 125 mg/kg feed x 2.5%), 375 µg/kg (0.10 x 125 mg/kg feed × 3%) and 625 µg/kg (0.10 x 125 mg/kg feed × 5%) respectively.

Cannavan et al. (2000) showed a linear relationship between nicarbazin feed intake and levels of DNC in eggs that could be described by the equation below. Further they demonstrated that nicarbazin levels in feed above 2 mg/kg results 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

From above equation, DNC residues in egg of 61.5, 158, 190 and 318 µg/kg would be anticipated at feed carry-over of 1, 2.5, 3 and 5% of the maximum authorised level of 125 mg/kg.

Option 2

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

Step 3. Action levels

The anticipated nicarbazin residue levels in eggs calculated by using the median TF and assuming hypothetical carry-over rates **(Option 1)** and at the maximum concentration in feed from feed mill studies **(Option 2)** are summarized in **Table 5**. Nicarbazin residue levels in egg at 1, 2.5, 3 and 5% hypothetical carry-over levels would be 125, 312.5, 375 and 625 µg/kg, respectively **(Option 1)** and at 2.2 mg/kg of carry-over level in feed 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)	2.5% (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

In the current example, anticipated nicarbazin residue level of 220 µg/kg was chosen as the appropriate value to use in the human exposure assessment based on the feed mill studies **(Option 2).**

If there are no data demonstrating 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 if CCRVDF should consider setting action levels.

Step 4. Human dietary exposure assessment

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.

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.

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).**

As a marker residue to total residue (MR:TR) ratio is not available for eggs, the lowest MR:TR 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)	MR:TR	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

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

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

In this pilot study, it is proposed to establish action level of 0.220 mg/kg for nicarbazin in eggs from laying hens as non-target animals to accommodate the presence of nicarbazin as a result of unavoidable and unintended nicarbazin carry-over in animal feed **(Table 7)**. This is in line with similar limits established by 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)		

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Note: This product is no longer approved for use in the United States.

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National and Regional Guidelines

Canada

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

European Union

- European Commission. 2011. Regulation (EC) No 574/2011 of 16 June 2011 amending Annex I to Directive 2002/32/EC of the European Parliament and of the Council as regards maximum levels for nitrite, melamine, Ambrosia spp. and carryover of coccidiostats or histomonostats in non-target feed. Off J Eur Commun. L40:19–25.
- COUNCIL DIRECTIVE (90/167/EEC) of 26 March 1990 laying down the conditions governing the preparation, placing on the market and use of medicated feedingstuffs in the Community
- DIRECTIVE 2002/32/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 7 May 2002 on undesirable substances in animal feed (http://eur-lex.europa.eu/legal-content/DE/TXT/HTML/?uri=CELEX:32002L0032&from=DE)
- COMMISSION DIRECTIVE 2009/8/EC of 10 February 2009 amending Annex I to Directive 2002/32/EC of the European Parliament and of the Council as regards maximum levels of unavoidable carry-over of coccidiostats or histomonostats in nontarget feed LexUriServ.do (europa.eu)
- COMMISSION REGULATION (EC) No 124/2009 of 10 February 2009 setting maximum levels for the presence of coccidiostats or histomonostats in food resulting from the unavoidable carry-over of these substances in non-target feed
- Document EUR-Lex - 52014PC0556
  Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND THE COUNCIL on the manufacture, placing on the market and use of medicated feed and repealing Council Directive 90/167/EEC (http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52014PC0556&qid=1444290152009&from=DE)
- Feed Hygiene Regulation (EC) No 183/2005: Annex II provides among others that “Technical or organisational measures must be taken to avoid or minimise, as necessary, any cross-contamination and errors.”
- European Feed Manufacturers Guide for good Hygiene Practice for the manufacturing of feed for food producing animals (EFMC): this guide is meant to help operators meeting the requirements of the EU Feed Hygiene Regulation. It includes provisions for the prevention and minimisation of carry-over, including guidance for the measurement of premises-bound carry-over. This includes also definitions of carry-over and cross-contamination.

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).										

APPENDIX II
LIST OF PARTICIPANTS

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

MEMBER COUNTRY/ORGANIZATION[1]	**OBSERVER**[2]
1. Australia	1. IFIF
2. Canada	
3. Chile	
4. Costa Rica	
5. European Union	
6. France	
7. Germany	
8. Italy	
9. Japan	
10. Mexico	
11. New Zealand	
12. Nigeria	
13. Norway	
14. Sweden	
15. USA	

[1] Please contact the focal point of the Member Country or Observer Organization for the details of the delegates. The list of Codex contact points for members are available from the Codex website at:
http://www.fao.org/fao-who-codexalimentarius/about-codex/members/en/
http://www.fao.org/fao-who-codexalimentarius/about-codex/observers/observers/obs-list/en/