CODEX ALIMENTARIUS COMMISSION

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Food and Agriculture Organization of the United Nations

World Health Organization

Viale delle Terme di Caracalla, 00153 Rome, Italy - Tel: (+39) 06 57051 - E-mail: codex@fao.org - www.codexalimentarius.org

**Agenda Item 10** **CX/RVDF 23/26/11**

**JOINT FAO/WHO FOOD STANDARDS PROGRAMME**

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

**26th Session**
**13-17 February 2023**
**Portland, Oregon, United States of America**

# PRIORITY LIST OF VETERINARY DRUGS FOR EVALUATION OR RE-EVALUATION BY JECFA

**Comments in reply to CL 2022/72-RVDF**

*submitted by*
*Brazil, Chile, Costa Rica, Kenya, Norway, Peru, Republic of Korea, Uganda and the International Commission for Uniform Methods of Sugar Analysis (ICUMSA)*

## Background

1. This document compiles comments received through the Codex Online Commenting System (OCS) in response to circulat letter CL 2022/72-RVDF[1] issued in October 2022. Under the OCS, comments are compiled in the following order: general comments are listed first, followed by comments on specific sections.

## Explanatory notes on the annexes

2. Comments submitted through the OCS are hereby attached as Annexes I, II, III and IV and are presented in tabulated format. Comments on Part I are compiled according to the template for submission of requests for veternary drugs for evaluation/re-evaluation by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

[1] http://www.fao.org/fao-who-codexalimentarius/resources/circular-letters/en/
http://www.fao.org/fao-who-codexalimentarius/committees/committee/related-circular-letters/en/?committee=CCRVDF

**Annex I**

**GENERAL COMMENTS**

| COMMENTS | MEMBER / OBSERVER |
|---|---|
| Brazil would like to inform that we have no proposals for veterinary drugs to be included in the priority list for subsequent recommendation to JECFA for evaluation or re-evaluation.<br>We are discussing with the industry and national authorities the possibility of sending complementary data to the drugs that are currently in the priority list, including related Brazilian GVPs. | **Brazil** |
| Chile Agradece la oportunidad de dar respuesta a esta carta circular y desea enviar una actualización de la información comprometida para aportar datos para la evaluación de amoxicilina que se acordó mantener en la lista de prioridades Parte II. Medicamentos veterinarios para los que debería confirmarse la disponibilidad de datos en la próxima reunión del CCVRDF. | **Chile** |
| Costa Rica quisiera apoyar el trabajo en las prioridades y ratificar la necesidad de los LMR para las moléculas propuestas; sin embargo, no disponemos de datos para aportar. No obstante, considera importante concluir con el desarrollo de esos LMRs. | **Costa Rica** |
| Position: Kenya agrees for veterinary drugs to be included to the priority list as per the template. | **Kenya** |
| No formatting corrections noted. | **ICUMSA** |

**SPECIFIC COMMENTS**

**Part I. Veterinary drugs for inclusion in the Priority List for JECFA evaluation/re-evaluation**

| | | |
|---|---|---|
| 1. | Miembro o miembros que remiten la petición de inclusión: Chile | **Chile** |
| 2. | Nombres del medicamento veterinario: Amoxicillin 50% | |
| 3. | Nombres comerciales<br>Primavet 50% (Centrovet)<br>Vetrimonix 50% (Ceva Santé animale)<br>Neumotona 50% (Veterquimica)<br>Amoxyvet (Intermedicavet)<br>Amoxy-50 (Zagro) | |
| 4. | Nombres químicos y número de registro CAS<br>(2S,5R,6R)- 6-{[(2R)-2-amino- 2-(4-hydroxyphenyl)-acetyl]amino}- 3,3-dimethyl- 7-oxo- 4-thia- 1-azabicyclo[3.2.0]heptane- 24-carboxylic acid | |
| 5. | Nombres y direcciones de los principales productores<br>Centrovet Ltda.<br>Avda. Los Cerrillos 602, Cerrillos, Santiago, Chile www.centrovet.com<br>Veterquimica S.A.<br>Camino a Lonquén 10387, Maipú, Santiago, Chile www.veterquimica.com<br>Ceva Sante Animale<br>Z.I. Tres Le Bois 22600, Loudéac, Francia | |
| 6. | Identificación del problema de inocuidad alimentaria (peligro de residuo)<br>Amoxicillin is a broad-spectrum antibiotic widely used for treating both human and animal diseases, and it belongs to a group that are excreted unchanged within urine and faeces; therefore, it is possible to find traces of this drug or its degradation products in environmental water bodies. In water, it is rapidly degraded by biotic and abiotic factors, yielding different intermediate products; these are suspected of being more resistant to degradation, and potentially more toxic, than the parent compound.<br>Amoxicillin may bioaccumulate in muscle tissues, with the possibility of the occurrence of these drugs in food, leading to a passive consumption of this antibiotic resulting in undesirable effects on consumer health such as immunoallergic responses. However, the main problem related with the presence of this antimicrobial compounds in tissues is the possibility of inducing bacterial resistance genes. | |
| 7. | Evaluación respecto de los criterios para la inclusión en la lista de prioridades<br>Amoxicillin, has been assessment twice by JECFA, 75 (2011) and 85 (2017) meetings. It currently MRLs for cattle, sheep, pigs and fish has been established, however, there is no Codex MRL in broiler chicken tissues.<br>Chile at CCRVDF24, after the discussion of "DATABASE OF COUNTRY MRL NEEDS (Agenda Item 11)", offered to develop dossiers to support the JECFA assessment for amoxicillin in poultry.<br>Chile proposes a reevaluation of this drug. GVPs were established and there are three products registered in the country for use in broiler chickens.<br>Verified maximum residue limits are necessary to ensure food safety for domestic use and protect the commercial destinations of edible broiler chicken tissues. | |
| 8. | Justificación para el uso<br>For the treatment of Staphylococcosis and Avian Streptococcosis (Staphylococcus spp., Streptococcus spp.), Fowl Cholera (Pasteurella multocida), Infectious Coryza (Avibacterium paragallinarum), Avian Colibacillosis (Escherichia coli), Avian Salmonellosis and Paratyphosis (Salmonella spp.) and Clostridium perfringens. | |

9. Patrón de uso veterinario, incluyendo la información sobre los usos aprobados, si estuviera disponible (debería incluir etiquetas de producto u otras pruebas que acrediten que posee una autorización oficial de uso)

Registered products are authorized for oral administration, dissolved in drinking water.
Dosage of Amoxicillin 20 mg per kg bodyweight (bw) for day for 5 - 7 days.

10. Productos para los que se requieren LMR del Codex

Muscle, liver, kidney and skin and fat in natural proportions of broiler chickens.

12. Países en los que el medicamento veterinario está registrado

European Union, Canada and Chile.

13. LMR nacionales o regionales o cualquier otra tolerancia aplicable

European Medicines Agency (EMA)
Muscle 50 µg/kg
Liver 50 µg/kg
Skin and fat 50 µg/kg
Kidney 50 µg/kg

14. Lista de datos disponibles (farmacología, toxicología, metabolismo, eliminación de los residuos, metodologías analíticas) (debería incluir una lista de los datos disponibles con los títulos completos de los estudios y si el compuesto también está registrado como plaguicida y, según proceda, si ha sido evaluado o programado para su evaluación o reevaluación por la JMPR)

A novel developed optimized and validated analytical methodologies for the detection of beta-lactams (amoxicillin) in edible (muscle, liver, kidney and fat) and feathers of broiler chickens.

An extraction method was developed for the detection and quantification of Amoxicillin residues in broiler chicken muscle and skin plus fat matrices. This was based on the publication of Benito-Peña et al., 2009 and Gajda et al., 2019. The analysis will be performed by high-performance chromatography coupled to tandem mass spectrometry (API 5500, AB SCIEX®).

The methodology will be validated for the parameters of linearity of the calibration curve, trueness, precision, decision limit (CCα), matrix effect, specificity, stability and robustness, according to the recommendations of the European Union document: 2021/808/CE “Commission Implementing Regulation (EU) 2021/808 of 22 March 2021 on the performance of analytical methods for residues of pharmacologically active substances used in food-producing animals and on the interpretation of results as well as on the methods to be used for sampling and repealing Decisions 2002/657/EC and 98/179/EC”.

In parallel, a methodology for the analysis of amoxicillin in kidney and liver is being optimized. However, the extraction of this compound has been more complicated to implement due to the properties of the analyte, such as its stability, interaction with these matrices and its protein binding capacity, among others.

A depletion study of amoxicillin in muscle, liver, kidney and skin and fat in natural proportion, of broiler chicken treated with isotopically labelled standards.

In order to determine the amoxicillin depletion time in the study matrices, an in vivo assay was performed with broiler chickens. For this, the birds were treated with a 50% amoxicillin pharmaceutical formulation, therapeutically as indicated on the label.

The study was based mainly on a trial with 40 broiler chickens of Ross 308 genetics, which were raised until 42 days of age, controlling temperature and relative humidity according to the physiological requirements of the birds, as well as drinking water and feed ad libitum, according to their nutritional requirements. These were kept from the first day of life in rearing batteries with a raised wire floor. The chicks were randomly divided from day 21 of life into a treatment group and a control group. The treatment group consisted of 30 birds treated with amoxicillin trihydrate 50% (authorized and described in the Register of Veterinary Medicines of the Agriculture and Livestock Service to be administered to broilers) at a therapeutic dose of 40 mg/kg/day for 7 days by orogastric tube, while the control or blank group consisted of 10 birds that did not receive treatment. After treatment, the matrices of interest were sampled on days 1, 2, 5, 9 and 18.

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| For each sampling point, six samples of muscle, liver, kidney and fat plus skin were obtained. Once the solid-liquid extraction of amoxicillin residues from the study matrices has been performed, as indicated in the previous point, the samples are analyzed by HPLC-MS/MS in order to obtain the concentrations of these analytes, using the standards Amoxicillin (certified with purity greater than 95%) and Amoxicillin D4 (as internal standard).<br>The study has the Biosafety Certificate Nº184 of the Biosafety Committee of the Faculty of Veterinary and Livestock Sciences of the University of Chile, and the certificate Nº 23643 – VET – UCH of the Institutional Animal Care and Use Committee (CICUA), issued by the same faculty. The euthanasia method was guided according to the recommendations of "The AVMA Guidelines for the Euthanasia of Animals" (2013), and Regulation No. 1099/2009 associated with the protection of animals at the time of killing of the European Commission (2009).<br>For the depletion study and the determination of the withdrawal period in the matrices, the guidelines of the document "Guideline on determination of withdrawal periods for edible tissues" of the European Medicines Agency (2018) will be followed.<br>15. Fecha en que los datos podrían remitirse al JECFA<br>A novel developed optimized and validated analytical methodologies for broiler muscle, and skin and fat: December 2023<br>A novel developed optimized and validated analytical methodologies for broiler liver and kidney: July 2024<br>A depletion study of amoxicillin in muscle, and skin and fat in natural proportions, of broiler chicken: July 2024<br>A depletion study of amoxicillin in liver and kidney, of broiler chicken: July 2024<br>It is important to consider that we are currently working on the extraction method for broiler chicken liver and kidney matrices, so the dates of the validation and depletion study are subject to the achievement of the development of the method. | |
| No se tiene observaciones como tampoco se propone medicamentos veterinarios para su inclusión en la lista de prioridades. | **Peru** |
| The Republic of Korea requests to include two(2) veterinary drugs, Clopidol and Fumagillin, in the Priority List for JECFA evaluation/re-evaluation.<br>**Information on Clopidol for Prioritization by CCRVDF is the following:**<br>*Administrative Information*<br>1. Member submitting the request for inclusion: Republic of Korea<br>2. Veterinary drug name: Clopidol (3-5-dichloro-2,6-dimethyl-4-pyridinol)<br>3. Trade names: Daehan-Clopidol<br>4. Chemical names and CAS registry number: Clopidol, 2971-90-6<br>5. Names and addresses of basic produces: Daehan Nupharm, 66 Jeyakgongdan 1-gil Hyangnam-eup, Hwasung-si, Gyeonggi Province, RoK<br>*Purpose, Scope and Rationale*<br>6. Identification of the food safety issue: Residue hazard<br>7. Assessment against the criteria for the inclusion on the priority list: ADI, MRLs for chicken muscle, liver, fat, kidney<br>*Risk Profile Elements*<br>8. Justification for use - Prevention and treatment of coccidiosis in broilers caused by E. tenella, E. necatrix, E. acervulina, E. mivati and E. brunetti - Prevention of leucocytozoonosis in broilers<br>9. Veterinary use pattern, including information on approved uses if available:- Incorporate it in feeds at 500g~1kg/ton of feed<br>10. Commodities for which Codex MRLs are required: Chicken muscle, liver, fat, kidney<br>*Risk Assessment Needs and Questions for the Risk Assessors*<br>11. Specific request to risk assessors: ADI evaluation, Residue depletion, MRL evaluation Available Information<br>12. Countries where the veterinary drugs are registered: Republic of Korea | **Republic of Korea** |

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|---|---|
| 13. National/Regional MRLs or any other applicable tolerances: 5.0mg/kg for poultry muscle, 20mg/kg for poultry liver, 5mg/kg for poultry fat, 20mg/kg for poultry kidney as RoK's national provisional MRLs<br>14. List of data available: Toxicological data Rodent Oral acute toxicity data (Rats)Rodent 90-day repeat oral toxicity data (Rats)Genotoxicity data (Ames' assay, In vitro chromosomal aberration assay, in vivo micronucleus assay)<br>Developmental toxicity data (Rats, Oral, Maternal, and fetal toxicity)- Residue depletion dataBroiler residue depletion dataTimetable<br>15. Date when data could be submitted to JECFA: Until July 31 2023<br>**Information on Fumagillin for Prioritization by CCRVDF is the following:**<br>*Administrative Information*<br>1. Member submitting the request for inclusion: Republic of Korea<br>2. Veterinary drug name: Fumagillin dicyclohexylamine<br>3. Trade names: Fumidil-B<br>4. Chemical names and CAS registry number: Fumagillin, 23110-15-8<br>5. Names and addresses of basic produces: KBNP, 415 Heungandae-ro, Dongan-gu, Anyang-si, Gyeonggi Province, RoK<br>*Purpose, Scope, and Rationale*<br>6. Identification of the food safety issue: Residue hazard<br>7. Assessment against the criteria for inclusion on the priority list: ADI, MRLs for honey and fish<br>*Risk Profile Elements*<br>8. Justification for use: Treatment for Nosema apis for honey bees, Prevention and treatment for infection by Sphaerospora renicola or Myxobolus cyprinid (carps), Pleistophor giardia or Myxobolus giardia (eels), or Sphaerospora sp or Myxobolus cerebralis (trouts)<br>9. Veterinary use pattern, including information on approved uses if available:<br>*Honey bees*: Dilute it in sugar water at certain rates (500 mg fumagillin dicyclohexylamine/7∼8 beekeepers/bee hive) and provide it once every week for 4∼8 weeks<br>*Fish*: Incorporate it in feeds at 300g~1kg/day/ton of fish weight or 1.2kg/ton of water weight for 5 days<br>10. Commodities for which Codex MRLs are required: Fish meat, honey<br>*Risk Assessment Needs and Questions for the Risk Assessors*<br>11. Specific request to risk assessors: ADI evaluation, residue depletion, MRL evaluation for honey and fish (trout or carp) Available Information<br>12. Countries where the veterinary drugs are registered: Republic of Korea<br>13. National/Regional MRLs or any other applicable tolerances: 0.01 mg/kg for fish as Korea's national provisional MRL<br>14. List of data available: Microbiological dataImpact on human intestinal microflora (NOEC)- Toxicological data Rodent 90-day repeat oral toxicity data (Rats) Genotoxicity data (Ames' assay, In vitro chromosomal aberration assay, in vivo micronucleus assay)<br>Developmental toxicity data (Rats, Oral, Maternal, and fetal toxicity)- Residue depletion dataHoney residue depletion dataFish residue depletion data (Trout)Timetable<br>15. Date when data could be submitted to JECFA: Until July 31, 2023 (All data upper mentioned except residue depletion data in trout)<br>Until September 30, 2023 (Residue depletion data in trout) | |
| Uganda is still building capacity to generate the relevant data/information required to complete the template Annexed to the Circular letter and submission to JECFA. Therefore, currently no compound is proposed to be included in the Priority List | **Uganda** |

**Part II. Veterinary drugs for which data availability should be confirmed at CCRVDF26**

| COMMENTS | MEMBER |
|---|---|
| Se ha gestionado la solicitud de datos toxicológicos a efectos de respaldar la evaluación de la norfloxacina. | **Peru** |
| Uganda is unable to support evaluation of the compounds (Amoxicillin, Ethoxyquin and Norfloxaci) due to lack of capacity to generate the relevant data. | **Uganda** |

**Part III. Veterinary drugs for which additional data / information is necessary to complete the JECFA evaluation**

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<tr><th>COMMENTS</th><th>MEMBER</th></tr>
<tr><td>
Imidacloprid<br>
Norway apologises for not being present at the 26th session of CCRVDF. We would though like to add some information regarding agenda items 3 and 10 and the need for more data on Imidacloprid.<br>
Regarding additional data for Imidacloprid, Norway supports the evaluation and can confirm that the sponsor has available relevant data for consideration by JECFA.<br>
We have responded to CL 2022/72 Part III providing information that additional data can be provided and would like to add the following:<br>
Imidacloprid has previously been granted prioritisation (JECFA 9th Meeting, List of Substances Scheduled for Evaluation and Request for Data, Published 01 September 2021). A dossier of information was provided to JECFA to allow the initial assessment. The Committee was unable to reach a conclusion on an ADI due to an outstanding question in relation to anti-microbial activity (JECFA 94th Meeting, Summary and Conclusions, Issued 03 June 2022). The sponsor has confirmed that they would like to provide supplementary information to answer the outstanding questions to enable JECFA to set and ADI and subsequently a Codex MRL.<br>
In addition to data already provided in November 2021 and evaluated by JECFA, the sponsor would be able to submit the final report on MIC analysis for imidacloprid and a response to the queries raised by JECFA following their evaluation, in response to the next call for data from JECFA:
<table>
<tr><th>Type</th><th>Title</th><th>Reference</th></tr>
<tr><td>Original</td><td>A., Pridmore. Determination of Minimal Inhibitory Concentrations (MICs) for imidacloprid and reference antimicrobial agent ampicillin against 90 bacterial strains representing the normal human intestinal microbiota.</td><td>A Pridmore. Report No. DWS/006/22, Don Whitley Scientific UK, 2022</td></tr>
<tr><td>Original</td><td>Written discussion regarding the issues raised in relation to antimicrobial activity and potential for resistance development.</td><td>Any references used in support of written discussion will be provided</td></tr>
</table>
We would like to request the working group on the priority list and the 26th session of CRVDF to take this into account in its discussions.
</td><td>Norway</td></tr>
<tr><td>No se tiene observaciones</td><td>Peru</td></tr>
<tr><td>Uganda is unable to support evaluation of the compounds(Ethion, Flumethrin and Fosfomycin ) due to lack of capacity to generate the relevant data</td><td>Uganda</td></tr>
</table>

**Part IV. Parallel review - Evaluation of a new compound**

| COMMENTS | MEMBER |
|---|---|
| No se cuenta con disponibilidad de datos o información pertinentes. | **Peru** |
| Uganda cannot confirm availability of information on good veterinary practice (GVP) | **Uganda** |