CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 8(a) **RVDF/22 CRD/25**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twenty-second Session

San José, Costa Rica, 27 April – 1 May 2015

REPLIES TO CL 2013/26-RVDF

(Replies from Algeria, Chile, Costa Rica, Norway, Republic of Korea, the United States of America)

ALGERIA

RENSEIGNEMENTS D'ORDRE ADMINISTRATIF

1 Membre(s) soumettant la demande d'inscription: Algérie

2 Noms des medicaments veterinaries: HISTOSTAT. 50

3 Marques: Alpharma – Zoetis.

4 Appelations chimiques et numéro de CAS: Nitarzone—n° 1198481.0 Zoetis

5 Noms et adresses des principaux fabricants: Alpharma – Zoetis

BUT, CHAMP D'APPLICATION ET RAISON D'ÊTRE

6 Identification de la question de la sécurité alimentaire (danger du aux résidus): produit renferme dans sa composition de l'Arsenic.

7 Conformité aux critéres justifiant l'inscription dans la liste de priorités : Peut être largement utilisé dans les élevages de dinde et volaille.

ELEMENTS DU PROFIL DE RISQUE

8 Justification de l'utilisation: C'est l'antiparasitaire utilisé pour lutter contre l'Histomonose chez la dinde.

9 Pratique d'utilisation vétérinaire, y compris des renseignements sur les usages approuvés, le cas échéant.

10 Produits pour lesquels des LMR codex sont demandées: : HISTOSTAT. 50

BESOINS D'ÉVALUATION DES RISQUES ET QUESTIONS ADRESSÉES AUX RESPONSABLES DE L'ÉVALUATION DES RISQUES.

11 Questions spécifiques adressées aux responsables de l'évaluation des risques: Quels sont les dangers lies à son utilisation notamment en matiére de LMR, délai d'attente.

RENSEIGNEMENTS DISPONIBLES

12 Pays où le medicament vétérinaire est homologue : U.S.A.

13 LMR nationales/régionales, ou tout autre seuil de tolerance applicable.

14 Liste des données disponibles: pharmacologie,toxicologie,metabolisme, dépletions des résidus, méthodes d'analyse.

CALENDRIER

15 Date à laquelle les données pourraient etre soumises au JECFA: mars 2015.

CHILE

INFORMACIÓN ADMINISTRATIVA:

1. Miembro o miembros que remiten la petición de la inclusión en la lista

Chile

2. Nombres del medicamento veterinario

Lufenuron

3. Nombres comerciales

No aplica

4. Nombres químicos y número de registro CAS

Nombre químico: N-[2,5-Dichloro-4-[(2R S)-1,1,2,3,3-hexafluoropropoxy)- phenyl]-3-(2, 6-difluorobenzyl) urea

Nº CAS: 103055-07-8

5. Nombres y direcciones de los productores básicos

La información será entregada al JECFA junto con el resto de los antecedentes solicitados.

PROPÓSITO, ÁMBITO DE APLICACIÓN Y JUSTIFICACIÓN:

6. Identificación del problema de inocuidad alimentaria (peligro de residuo)

Actualmente existen estudios toxicológicos sobre este compuesto que demuestran que el Lufenuron no es tóxico agudo, no irrita piel u ojos, no es mutagénico, solo un sensibilizador leve de piel. Estudios en roedores y no roedores muestran que este compuesto no es teratogénico así como tampoco carcinogénico ni toxico a nivel reproductivo.

Los efectos neurológicos solo se han visto en estudios crónicos y subcrónicos a altas dosis y después de una exposición por tiempos prolongados.

El IDA establecido por la U.E. es de 0,015mg/kg pv.

7. Evaluación respecto de los criterios para la inclusión en la lista de prioridades

- Este compuesto es una alternativa viable y novedosa para el control eficaz de la Caligidosis, constituyendo una herramienta terapéutica clave para la producción de salmónidos, en virtud a sus propiedades favorables en cuanto a su bajo impacto ambiental dado a su aplicación en primeras etapas del ciclo productivo; así como también a su baja metabolización; condiciones que hoy en día no son entregadas por los productos existentes en el mercado tanto nacional como internacional para el control de Caligidosis. Asimismo, este compuesto aún no ha sido registrado en ningún país del mundo por lo que establecer el nivel máximo de residuo en salmónidos facilitaría su registro a nivel local e internacional.
- El control efectivo de los piojos de mar en salmonídeos se ha ido haciendo más difícil debido al desarrollo de resistencia a algunos de los productos existentes en el mercado, lo que no puede excluirse del análisis de la situación nacional. La necesidad de un nuevo activo que provea de un control efectivo y de larga duración se necesita urgentemente para asegurar la sustentabilidad de la industria salmonicultora.

ELEMENTOS DEL PERFIL DE RIESGO:

8. Justificación para el uso

- Lufenuron corresponde a un antiparasitario externo, recomendado para ser utilizado en el control y prevención a largo plazo de la infestación por piojo de mar (*Leophtheirus salmonis* y *Caligus sp)*, en Salmón del Atlántico (*Salmo salar*) y Trucha arcoíris (*Oncorhyncus mykiss*). Es eficaz en el control de Caligidosis durante su **estadio juvenil**, ya que a diferencia de otros antiparasitarios actualmente registrados en Chile (piretroides y órganos fosforados), actúa a nivel central del parásito, inhibiendo la producción de quitina impidiendo de este modo la elaboración de exoesqueleto y por ende la muda, generando así la muerte del parásito.
- Se caracteriza por ser aplicado en estanques, es decir, en la fase de agua dulce, así como también por su baja metabolización y mayor persistencia en el pez lo que conlleva a un bajo impacto ambiental y a una mayor protección de los salmónidos.
- Su aplicación durante las primeras etapas del ciclo productivo del salmón, permitiría disminuir la cantidad y frecuencia de uso de los productos actualmente registrados para su aplicación directa en mar, lo cual se asocia a menor impacto ambiental y menor riesgo de presencia de residuos en productos.
- Se considera que el parasitismo por los piojos de mar, es la enfermedad más significativa y diseminada en los salmonideos de cultivo, afectando negativamente el bienestar de los peces y la productividad de la industria. El estrés ocasionado por el parásito, altera el comportamiento de alimentación del pez, disminuye la respuesta inmune de éste y por lo tanto, incrementa la susceptibilidad a otras enfermedades infecciosas, ocasiona reducción del crecimiento y un aumento de los índices de conversión alimenticia. Las lesiones de la piel causadas por los parásitos en los casos severos pueden resultar en fallas de la osmoregulación o infecciones secundarias.

9. Patrón de uso veterinario, incluyendo la información sobre los usos aprobados, si estuviera disponible

- El producto se encuentra indicado para la prevención y control de infestaciones producidas por el piojo de mar, especies *Lepeophtheirus salmonis* y *Caligus* en salmones de cultivo.
- El alimento medicado es dado a los peces durante un período de 7 días antes de ser trasladados al mar a una dosis de 5 mg/kg/día de peso corporal y el alimento es medicado a una tasa de inclusión que ha sido calculada para alcanzar este nivel. Sin embargo, en algunos casos cuando la tasa de alimentación esperada es interrumpida, el período de alimentación podría necesitar ser extendido hasta un máximo de 14 días para asegurar que los peces reciban la dosis terapéutica completa.

- Lufenuron (AH-2178) es agregado en la premezcla al 10%. El alimento medicado es preparado mediante la adición de la premezcla en alimentos comerciales para peces. El alimento medicado con AH-2178 debe ser preparado solamente en las instalaciones de empresas productoras de alimento para peces que estén autorizadas para medicar alimento, no en los centros de cultivo.
- La tasa estándar de incorporación es de 5 kg de premezcla en 1000 kg de alimento pre-traslado al mar, pero esta tasa podría variar dependiendo del sistema de alimentación de los peces.
- Para garantizar eficacia en la prevención y control de infestaciones producidas por el piojo de mar, se recomienda que el producto AH-2178 sea usado de acuerdo con las siguientes consideraciones:
  - Administración de la dosis correcta durante al menos el período de 7 días completo.
  - Medicación de una cantidad apropiada de alimento para asegurar un consumo completo y homogéneo.
  - Cuidadosas prácticas de alimentación para monitorear el comportamiento alimentario de los peces.
  - Uso del producto en la ausencia de cualquier enfermedad concomitante que afecte el apetito.

10. Productos para los que se requieren LMRs del Codex

Especie: Salmónidos

Tejido: Músculo y piel en proporciones naturales

NECESIDADES DE EVALUACIÓN DE RIESGOS Y PREGUNTAS PARA LOS EVALUADORES:

11. Petición específica para los encargados de la evaluación de riesgos

Se le solicita a JECFA determinar un IDA y establecer LMRs en salmónidos.

INFORMACIÓN DISPONIBLE:

12. Países donde el medicamento veterinario está registrado

A la fecha el medicamento no está registrado en ningún país.

13. LMRs nacionales **o regionales o cualquier otra tolerancia aplicable**

El 13 de Septiembre de 2014 fue publicado en el Diario Oficial de la Unión Europea la fijación de un LMR para Lufenuron en peces (fin fish), en esta publicación, se establece que se hará aplicable a partir del 12 de Noviembre de 2014.

Tabla n°1. LMRs Unión Europea para Lufenuron

Sustancia Farmacológicamente Activa	Residuo	Especie animal	LMRs	Tejidos blanco	Otras disposiciones	Clasificación Terapéutica
Lufenuron (Isómeros-RS)	Lufenuron (Isómeros-RS)	Peces	1350 µg/kg	Músculo y piel en proporciones normales	Nada	Antiparasitario/ Agentes (activos) frente a los ectoparásitos

Referencia: Tabla N° 1 (sustancias permitidas) del Anexo de la Regulación de la Comisión (EU) N°37/2010.

También, se ha ingresado la información necesaria para solicitar el establecimiento de LMRs en Japón, el que de acuerdo a los antecedentes, se estima que sería resuelto el primer trimestre de 2015.

Adicionalmente, se puede señalar, que en Octubre de 2014 se solicitó un “Import Tolerance” para la sustancia al FDA de Estados Unidos.

14. Listas de datos disponibles (farmacología, toxicología, metabolismo, agotamiento de los residuos, metodologías analíticas)

Se adjunta **Anexo** que contiene la lista de los datos disponible

ESQUEMA CRONOLÓGICO:

15. Fecha en que los datos podrían remitirse al JECFA

El paquete de datos está disponible y será presentado en cuanto sea solicitado.

Anexo

Información de Seguridad

Absorción, Distribución, Metabolismo y Excreción (DME) en ratas
Farmacocinética en ratas
Absorción, Distribución, Metabolismo y Excreción (DME) en perros

Farmacocinética en cabras y gallinas (lactancia y postura)
Absorción y Caracterización en bluegill sunfish
Acumulación y eliminación en featherhead minnow
Toxicidad e irritación en roedores y lagomorfos
Toxicidad oral en perros
Reproducción y teratología en roedores y lagomorfos
Ames test
Estudios de mutación celular y cromosómica en células de hámster
Universal Sorption Device- UDS testing en células humanas
UDS testing – hepatocitos de rata
Test de micronucleus en ratón
Carcinogenicidad en roedores
Efectos endocrinológicos en ratas
Resumen de Farmacología General
Lotes de Lufenuron utilizados para toxicología
Identificación precisa del producto y su sustancia activa
Resumen Crítico y Detallado de la Información de Seguridad, Presentación MRL Unión Europea

Información de Residuos

Absorción, Distribución, Metabolismo y Excreción (DME) en ratas
Farmacocinética en ratas
Absorción, Distribución, Metabolismo y Excreción (DME) en perros
Farmacocinética en cabras y gallinas (lactancia y postura)
Plan de Estudios de eficacia de Lufenuron administrado en alimento en salmones(estudio de campo)
Plan de Estudios de eficacia de Lufenuron administrado en alimento en salmones. Anexos reportes bioanalíticos
Estudios de eficacia de Lufenuron administrado en alimento en salmones (estudio de campo). Evaluación estadística
Método analítico y validación del método para la determinación de Lufenuron en salmonídeos
EFSA Revisión Lufenuron
Lufenuron – Absorción y cinética de deplesión desde el tracto gastrointestinal en la rata
Identificación precisa del producto y su sustancia activa: residuos
Resumen Crítico y Detallado de la Información de Residuos, Presentación MRL Unión Europea
Absorción, Distribución, Metabolismo y Excreción (DME) Reporte en Salmón del Atlántico

COSTA RICA

Costa Rica agradece la oportunidad de expresar sus comentarios sobre la lista de prioridades de medicamentos veterinarios, sin embargo se le imposibilita cumplir con los requisitos que existen por el CCRDVF para que un país pueda solicitar la inclusión de un medicamento veterinario a lista de prioridades así como, presentar los estudios científicos para dicha evaluación. Por lo anterior, se nos dificulta proponer prioridades.

NORWAY

Lufenuron

ADMINISTRATIVE INFORMATION

1. Member(s) submitting the request for inclusion

Norway

2. Veterinary drug names

Lufenuron

3. Trade names

TBD

4. Chemical names and CAS registry number

1-[2,5-Dichloro-4-[(2R S)-1, 1,2,3,3,3-hexafluoropropoxy]phenyl]-3-(2,6-difluorobenzoyl)urea

CAS registry #103055-07-8

5. Names and addresses of basic producers

There are several producers or the active substance.

PURPOSE, SCOPE AND RATIONALE

6. Identification of the food safety issue (residue hazard)

7. Assessment against the criteria for the inclusion on the priority list

This compound meets the criteria for inclusion in the priority list for the following reasons:

- A member is proposing the compound for evaluation (Norway)
- The compound is intended for use in the long-term prevention and control of sea lice infestation with *Lepeophtheirus salmonis* and *Caligus* species, on farmed Atlantic salmon (*Salmo salar*) and Rainbow trout (*Oncorhynchus mykiss*).
- Sea lice are believed to cause the most significant and widespread disease of farmed salmonids, negatively affecting fish welfare and industry productivity. Lice feeding behaviours increase stress and decrease the immune response of the fish, which can result in increased susceptibility to other diseases, reduced growth and increased feed conversion ratio. The skin lesions caused by the parasites may in severe cases result in death of the fish due to osmoregulatory failure or secondary infections.
- The effective control of sea lice in Atlantic salmon farms is increasingly difficult due to drug resistance to some marketed products. The need for novel active ingredients providing effective and to some extent long-lasting control of sea lice is urgently needed to ensure the sustainability of the farmed salmonid industry.
- Clinical field studies are already underway in key markets.
- Salmon fillet is traded globally but only produced by a few countries.

RISK PROFILE ELEMENTS

8. Justification for use

Lufenuron is a benzoylphenyl-urea, a well-known class of compounds used in animal health and crop protection; the compound disrupts the formation of chitin, most probably by enzymatic interference, impacting critical stages of formation of new cuticles in sea lice. As such, developmental stages of sea lice fail to molt and ultimately die.

The end-use product is intended to be applied as a pre-mix for medicated feed and fed to juvenile fish whilst at a freshwater hatchery. Preliminary studies demonstrated the end-use product provides 6-9 months of protection against infestation with sea lice once the fish are transferred to sea cages.

Sea lice resistance to many of the licensed therapeutic options for the control of sea lice is widespread. It is therefore anticipated that the compound will provide a valuable tool in the management of sea lice at commercial fish farms globally.

9. Veterinary use pattern, including information on approved uses if available

The compound is intended to be applied as a pre-mix for medicated feed. The proposed target dose of lufenuron is 5 mg/kg body weight/day for 7 days, for a total dose of 35 mg/kg body weight, administered to juvenile Atlantic salmon and Rainbow trout at freshwater hatchery.

The number of days required to administer the target dose may vary due to sudden changes in water temperature or quality, or to unexpected fluctuations in appetite, and therefore the treatment period may be extended to 10 days to ensure homogeneous uptake in large populations of salmonids.

The feed will be medicated to a standard inclusion rate or in accordance with an inclusion rate specified by veterinary prescription.

10. Commodities for which Codex MRLs are required

Fillet (muscle plus overlying skin with scales in natural proportions)

Please refer also to attached CVMP document.

RISK ASSESSMENT NEEDS AND QUESTIONS FOR THE RISK ASSESSORS

11. Identify the feasibility that such an evaluation can be carried out in a reasonable framework

12. Specific request to risk assessors

AVAILABLE INFORMATION

13. Countries where the veterinary drugs are registered

Not applicable yet. Novartis Animal Health is planning and conducting clinical field studies to support registration of the product as soon as possible.

14. National/Regional MRLs or any other applicable tolerances

A European MRL has been established:

Pharmacologically active Substance	**Marker residue**	**Animal Species**	**MRL**	**Target Tissues**	**Other Provisions (according to Article 14(7) of Regulation (EC) No 470/2009)**	**Therapeutic Classification**
Lufenuron (RS-isomers)	Lufenuron (RS-isomers)	Fin fish	1350 µg/kg	Muscle and skin in natural proportions	NO ENTRY	Antiparasitic agents/Agents (acting) against ectoparasites

15. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available

A list of available data is attached with this request.

TIMETABLE

16. Date when data could be submitted to JECFA

The data could be submitted at any time when requested.

[1] When preparing a preliminary risk profile, Member(s) should take into account the updated data requirement, to enable evaluation of a veterinary drug for the establishment of an ADI and MRLs, published by JECFA.

Annex - List of available data

Safety documentation

ADME in rats
Pharmacokinetics in rats
ADME in dogs
Pharmacokinetics in goats and hens(lactation and laying)
Uptake and characterisation in bluegill sunfish
Accumulation and elimination in featherhead minnow
Toxicity and irritation in rodents and lagomorphs
Oral toxicity in dogs
Reproduction and teratology in rodents and lagomorphs
Ames test
Chinese hamster cell mutation and chromosome studies
UDS testing - human cells
UDS testing - rat hepatocytes
Micronucleus test – mouse
Carcinogenicity in rodents
Rat endocrinology effects
Summary of General Pharmacology
Lufenuron lots used for the Tox Reserve
Precise identification of the product and of its active substance
Lufenuron Detailed and Critical Summary Safety_EU MRL application

Residues documentation

ADME in rats
Pharmacokinetics in rats
ADME in dogs
Pharmacokinetics in goats and hens(lactation and laying)
Lufenuron in-feed efficacy in salmon (field study) study plan
Lufenuron in-feed efficacy in salmon (field study) Bioanalytical report appendices
Lufenuron in-feed efficacy in salmon (field study) statistical evaluation
Analytical method for Determination of lufenuron in salmonids and validation
EFSA review on lufenuron
Lufenuron - Absorption and depletion kinetics from the GI tract in the rat
Precise identification of the product and of its active substance:Residue
Lufenuron EU MRL residues Detailed and Critical Summary
ADME report in Atlantic salmon

Diflubenzuron

ADMINISTRATIVE INFORMATION

1. Member(s) submitting request for information

Norway

2. Veterinary drug names:

Diflubenzuron

3. Trade names:

Releeze 0.6 g/kg (EWOS AS), EWOS DFB (FAV Recalcine), Dimilin, Micromite, Adept, Du-Dim, Device, DU 112307, PH 60-40, TH 6040, ENT-29054, OMS 1804 (Crompton BV trade names and/or past development codes).

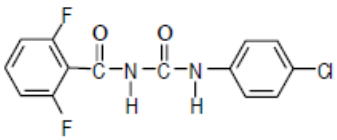
4. Chemical names:

IUPAC: 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea

CAS: N-[[(4-chlorophenyl)amino]carbonyl]-2,6-difluorobenzamide

CAS registry number: 35367-38-5

Structural formula:



Molecular formula:

$C_{14}H_9ClF_2N_2O_2$

5. Name and address of basic producers:

Dopharma BV

Zalmweg 24, 4941 VX Raamsdonksveer

The Netherlands

PURPOSE, SCOPE AND RATIONALE

6. Identification of the food safety issue (residue hazard)

Diflubenzuron, [1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl) urea] is an acyl urea derivative for use in the treatment of sea lice (*Lepeophtheirus salmonis* Krøyer) infestations in Atlantic salmon (*Salmo salar* Linné) on the Northern hemisphere and sea lice (*Caligus rogercresseyi)* infestation in salmon on the Southern hemisphere. Diflubenzuron is admixed as a 90% pre-concentrate in pelleted diet at a final concentration of 0.6 g diflubenzuron/kg. The intended oral dosage is 3-6 mg diflubenzuron/kg bdw/day during 14 consecutive days.

The substance is also used in agriculture, horticulture and forestry against larvae of *Lepidoptera, Coleoptera, Diptera, Hymenoptera* and in public health against larvae of mosquitoes and other noxious insects.

Diflubenzuron acts by interference with the synthesis of chitin. Demand for chitin synthesis is greatest at the moult between growth stages and hence parasites are killed due to disruption of the moulting process. The fatal effect occurs by the inability of the treated parasites to moult properly due to incomplete development of chitin, with subsequent collapse of the exoskeleton.

7. Assessment against the criteria for the inclusion on the priority list

The compound meets the criteria for inclusion on the priority list for the following reasons:

- A member state (Norway) is proposing the compound for evaluation
- The compound is approved for use in salmon farming in Norway and Chile
- Threshold levels for exposure has been established both in Norway, Island and EU (EEA), and by FAO

RISK PROFILE ELEMENTS

8. Justification for use

Sea lice (*L. salmonis* K.) infestation is causing significant losses in commercial farming of Atlantic salmon (*S. salar*) on the Northern hemisphere (Norway, Faeroe Islands, Scotland, Canada and USA). Spread of sea lice larvae to the environment is also posing an increasing treat to decimation of wild populations of both Atlantic salmon (*S. salar)* and sea trout (*Salmo trutta*), and in worst cases eradication of wild, local populations. Hence, treatment thresholds and coordinated treatment strategies have been established to reduce production of larvae from the salmon farms.

Sea lice (C. *rogercresseyi)* infestation is also causing significant losses in commercial farming of salmon in the Southern hemisphere (Chile).

Reduced sensitivity / drug resistance is an emerging problem in current sea lice treatment. Currently used therapeutics for bath treatments are organophosphates and synthetic pyrethroids. Avermectins and chitin inhibitors are used as oral treatments. Hydrogen peroxide is also used for bath treatment. It is important to vary treatment regimens and to avoid repeated use of one therapeutic group for long time periods. For effective sea lice management in salmon farms, there is a need to combine drug rotations with non-chemical strategies. An overview of sea lice treatment methods and consequences related to resistance development has been presented by Denholm et al. in 2002 and highlighted again by Igboeli et al. in 2014.

9. Veterinary use pattern, including information on approved uses if available

Releeze 0.6 g/kg “EWOS” has been granted marketing authorization (MA) from The Norwegian Medicines Agency (NoMA) in Norway. Approved indication for use is for treatment of Atlantic salmon (*S. salar*) against premature sea lice infestation (*L. salmonis* K.). Administration is done by dosing of medicated pellets containing 0.6 g diflubenzuron/kg at a daily rate of 0.5 – 1.0 % of bdw, corresponding to 3-6 mg/kg bdw/day for 14 consecutive days. Restrictions do apply for the use. Withdrawal time before slaughter is 105 degree-days.

EWOS DFB “FAV Recalcine“ is licenced for use in Chile by Servicio Agrícola y Ganadero (SAG). Recommended dosing is 6 mg/kg bdw/day for 14 consecutive days.

10. Commodities for which MRL’s are required

Pursuant to Commission Regulation (EU) 37/2010, ingredients in veterinary medicines intended for use in food producing animals must have established maximum residue levels (MRL). MRL for diflubenzuron was set pursuant to regulation (EU) 2377/90 (preceding (EU) 37/2010) to 1000 µg/kg for muscle/skin in natural proportions in 1988.

RISK ASSESSMENT NEEDS AND QUESTIONS FOR THE RISK ASSESSORS

11. Specific request to risk assessors

Diflubenzuron was evaluated by the FAO/WHO JMPR and WHO/IPCS in 1981, 1984, 1988, 2002 and 2004. The WHO hazard classification of diflubenzuron is: Unlikely to present acute hazard in normal use (WHO 2002), based on an acute oral LD_{50} of more than 4640 mg/kg body weight in rats.

The US EPA published a Re-registration Eligibility Decision for diflubenzuron in August 1997.

Diflubenzuron has been reviewed by the European Commission under Directive 91/414/EC, and an MRL pursuant to Directive 2377/90 was published in 1999.

Pursuant to Article 11 of Regulation (EC) No 470/2010, The European Commission has recently (2014) requested the CVMP to review its previous opinion for the establishment of maximum residue limits (MRLs) for diflubenzuron in view of concerns relating to the metabolite 4-chloroaniline and recent evaluations by the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA). The CVMP is seeking to obtain any relevant data available on the metabolism of diflubenzuron and the formation of the genotoxic metabolite 4-chloroaniline, species differences in the metabolism of diflubenzuron and their relevance in relation to human exposure to 4-chloroaniline, and the depletion of diflubenzuron in salmon or other fin fish species with information on relevant metabolites. Information is also sought on the possible effects of sample processing and storage on the formation of 4-chloroaniline.

AVALABLE INFORMATION

12. Countries where the drug is registered

Norway and Chile

13. National/Regional MRLs or any applicable tolerances

Norway, Island and EU (EEA): 1000 µg/kg for muscle and skin in natural proportions

14. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available

- Pharmacology:

The pharmacokinetic of diflubenzuron in Atlantic salmon (*S. salar*) has been studied by EWOS AS after both single oral dose (75 mg/kg/bdw) of radiolabelled (^{14}C) diflubenzuron and after a single intravenous and oral dose of 3 mg/kg/bdw. Absorption from the gastro-intestinal tract was only partial, and bioavailability in recommended dose was calculated to 31%. The absorption is considered to be dose dependant and saturable in Atlantic salmon (*S. salar*). Distribution followed a one-compartment open model with first order input and first order output with a lag time of 3.5 hours after oral administration. The mean peak plasma concentration (0.141µg/ml) was reached after 24 hours. Autoradiography showed highest concentrations in the fillet (10%) and radioactivity in the bile showed that the biliary route is the major excretory pathway.

- Toxicology:

The Joint FAO/WHO meeting on Pesticide Residues (JMPR) evaluated diflubenzuron in 1981, 1984 and 1985 and the International Programme in Chemical Safety (IPCS) in 1996. An ADI of 0.02 mg/kg/bdw/day based on NOELs for methaemoglobin formation in the submitted long-term toxicity/carcinogenicity studies in dogs, rat and mice. EMA recommended a toxicological ADI of 0.0124 mg/kg/bdw/day based on the mice studies and applying a safety factor of 100 when MRL was decided in 1999.

- Metabolism:

Metabolism of diflubenzuron in Atlantic salmon (*S. salar*) has been evaluated by EWOS AS in cooperation with Uniroyal Chemical BV in 1997 according to EEC Regulation No 762/92 and in compliance with Good Laboratory Practice (GLP). The aims of the study were:

  - To obtain total radiochemical depletion of ^{14}C-diflubenzuron following single and repeated administration to Atlantic salmon (*S. salar* L.).
  - To obtain a metabolic profile of ^{14}C-diflubenzuron in selected tissues, and to identify metabolites which were present at concentrations greater than 50 ppb, and to characterise metabolites, which were present at concentration greater than 10 ppb.

Diflubenzuron was found as the main total residual radioactivity (TRR) both in fillet and in liver corresponding to 94.8% and 72.7%, respectively, at day 1 after the repeated dosage regime. Concurrent values found in the single dose regime were 88.6 and 69.3% respectively. Four other minor components were also detected, one found to be 4-chlorophenyl urea (0.23 ppb in liver day four in the repeated dose group). It is postulated that the unknown substances are mono-hydroxylated products of diflubenzuron. All metabolites except diflubenzuron had disappeared from the tissues day 7 in both dosing regimens. Base hydrolysis of solid residues in liver revealed at least five components at levels <9 ppb. Three chromatographed with reference standards for diflubenzuron, 4-chlorophenyl urea, 4-chloraniline and two unknown substances. 4-chlorophenyl urea and several other components were also found in extracts from control incubations. It is therefore postulated that these residues can be artefacts produced in the alkaline extraction procedure rather than true metabolites.

- Residue depletion:

Several studies have documented depletion of diflubenzuron from Atlantic salmon (*S. salar*). It can be concluded that diflubenzuron should be considered marker residue and that there is low metabolism in Atlantic salmon.

Excretion from the tissues is rapid. Depending on dosage regime, only 25- 35% of radioactive dose is remaining 1 day following dosing. This portion has further declined to less than 1.5 % seven days after dosing. There is no evidence of enzyme induction in the fish, since elimination profiles in different dosage regimes are following the same pattern.

- Analytical method:

A routine analytical HPLC- method for detection and quantification of diflubenzuron in salmon tissues (fillet and liver) has been developed by EWOS AS in cooperation with Uniroyal Chemical BV. The limit of quantification (LOQ) has been determined to 0.05 mg/kg. The limit of detection (LOD) has been determined to 0.02 mg/kg. The method has been validated in the range 0.05 mg/kg to 5.0 mg/kg, but validation was not done in accordance with requirements in Volume 8: Notice to applicants and Guideline: Veterinary medicinal products; Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin. Validation of the method should be done for muscle and skin in natural proportions.

TIMETABLE

15. Date when data could be submitted to JECFA

The data could be submitted at any time when requested.

REFERENCES

1. Denholm, I., Devine, G.J., Horsberg, T.E., Sevatdal,. S., Fallang, A., Nolan, D.V. and Powell, R. Analysis and management of resistance to chemotherapeutants in salmon lice, *Lepeophtheirus salmonis* (Copepoda: Caligidae). Pest Management Science, 58 (2002) 528-536.

2. Igboeli, O.O., Burka, J.F and Fast, M.D. *Lepeophtheirus salmonis*: a persisting challenge for salmon aquaculture. Animal Frontiers vol. 4 no. 1 (2014) 22-32

Teflubenzuron

1. Member submitting the request for inclusion

Norway

2. Veterinary Drug Names

Teflubenzuron

3. Trade Names

Calicide (Canada, UK, Ireland)

Ektobann (Norway)

4. Chemical Names and CAS registry number

1-(3,5-dichloro-2,4-difluorophenyl)-3-(2,6-difluorobenzoyl)urea

CAS No 83121-18-0

5. Names and addresses of basic producers

UK:

Trouw (UK) Limited

Wincham, Northwich

Cheshire

CW9 6DF

UK

Ireland:

Trouw Aquaculture Ltd (T/A Skretting)

Roman Island

Westport

Co. Mayo

Ireland

Canada:

Skretting AS

1350 East Kent Avenue

Vancouver, B.C.

V5X 2Y2

Canada

Norway:

Skretting AS

Sjøhagen 15, P.Box 319

4002 Stavanger

Norway

A.1.1. Purpose, Scope and Rationale

6. Identification of the food safety issue (residue hazard)

EMEA summary report.

7. Assessment against the criteria for the inclusion on the priority list

- A member has proposed the compound for evaluation (Norway)

- A member has established good veterinary practices with regard to the compound

- The compound is available as a commercial product

- The compound is eliminated from the tissues quickly and is therefore a low risk for consumers

A.1.2. Risk Profile Elements

8. Justification for use

Control of sealice (*Lepeophtheirus salmonis*) in farmed Atlantic salmon (*Salmo salar*).

9. Veterinary use pattern, including information on approved uses if available

Teflubenzuron is added to the fish feed at the dose of 2 g per kilogram and offered to fish for 7 consecutive days. The therapeutic dosage is 10 mg TFBZ/kg body weight of fish per day for 7 days.

10. Commodities for which Codex MRLs are required

Muscle and skin of Atlantic salmon.

A.1.3. Risk assessment needs and questions for the risk assessor

11. Specific request to risk assessors

- Take into account residue pharmacokinetics when recommending MRLs that accommodate international uses of teflubenzuron.

Teflubenzuron has been reviewed by the FDA, CVMP/EMA, Irish Medicines Board, Veterinary Drug Directorate (UK), Health Canada and Norwegian Medicines Agency.

A.1.4. Available information

12. Countries where the veterinary drug are registered

UK, Ireland, Canada and Norway.

13. National/Regional MRLs or any other applicable tolerances

Table 1. Table is showing information about the countries were the veterinary drug are registered together with the MRLs and withdrawal.

Country	Product Name	API	Product description	MRL (ppm)	Withdrawal
UK	Calicide	Teflubenzuron	Medicine	0.5 skin and muscle combined	7 days
Ireland	Calicide	Teflubenzuron	Medicine	0.5 skin and muscle combined	45 degree days
Canada	Calicide	Teflubenzuron	Medicine	0.3 in muscle 3.2 in skin	11 days
Norway	Ektobann	Teflubenzuron	Feed + medicine	0.5 skin and muscle combined	96 degree days

MRL set in Europe by EMEA (1999).

FDA has given an import tolerance (2014) of 0.5 ppm. http://www.fda.gov/AnimalVeterinary/Products/ImportExports/ucm315830.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

14. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available

Toxicology was reviewed in the Joint FAO/WHO 1994 meeting and an ADI of 0.01 mg/kg bw established.

http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Reports_1991-2006/Report1994.pdf

Residues were reviewed in the Joint FAO/WHO 1994 meeting and further information was needed to continue the assessment.

http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Reports_1991-2006/Report1996.pdf

A list of pharmacology, metabolism, residue depletion and analytical methods is available.

Toxicology studies were already submitted for the Joint committee's 1994 meeting.

Timetable

15. Date when data could be submitted to JECFA

REPUBLIC OF KOREA

Amoxicillin

ADMINISTRATIVE INFORMATION

1. Member(s) submitting the request for inclusion

Republic of Korea

2. Veterinary drug names

Amoxicillin hydrate, Amoxicillin sodium

3. Trade names

(A) Amoxicillin hydrate by oral administration

1) Fish-Amoxcilin 100 (Nel biotech Co)
2) Susnayong Amoxin (Dawonchemical Co)
3) Amoxin 20for fish (Dawonchemical Co)
4) Susnayong Amoxin 40 (Dawonchemical Co)
5) GD-Amoxy 300 (Woosung Co)
6) Green Amoxipen (Jeibisolution Co)
7) Aqua amoxy 200-S (Komipharm Co)
8) Amovita-C (Komipharm Co)
9) AMOXYL SOLUBLE POWDER for Fish (Green cross Veterinary products Co)
10) Aqua amocillin (Daehan New Pharam Co)
11) Aqua amocillin 30% (Daehan New Pharam Co)
12) Aqua Amox (DongbuPharmhannong Co)
13) Amoxy Aqua (Samu median Co)
14) Amoxy 50 Aqua (Samu median Co)
15) Susanyong Amoxcin 200 (Seoul Vet Pharma co.,Ltd)
16) AUQA AMOXINGUARD-200 SOLUBLE POWDER (KOFAVET special,lnc.)
17) Susanyong Amoxcillin 20 gayongsan (SamyangAniPharm Co)
18) Aqua-Amoxan 100 (SF Co)
19) Amoxy-Pan (WooGene B&G Co)
20) FISH-AMOXIPOWER 200 (YuniBiotech Co)
21) Aqua Amoxicillin Powder (Eaglevet Co)
22) AmoxaFish (Ewha PharmTek Co)
23) WillowMarine Yuhan-Kymoxin Plus (Ewha PharmTek Co)
24) Fishmoxy 200 (Ewha PharmTek Co)
25) JinWoo Amoxicillin San(Fish) (JinWoo Vet.Pharm Co)
26) Aqua-powermoxin 200 (JinWoo Vet.Pharm Co)
27) Aqua chamshim amoxillin (CharmsinPharam Co)
28) Aqua chamshim amoxillin-200 (CharmsinPharm Co)
29) Aqua chamshim amoxillin-500 (CharmsinPharm Co)
30) Susanyong Amoxilate (HanGukSumVet Co)
31) Susanyong Amoxil 200 (SungWon Co)
32) AquaMox 200 (KOFAVET special,lnc.)
33) Amocshot A (CTCBio Co)

(B) Amoxicillin sodium by Upper intramuscular injection

1) Kamoxin Aqua injection (KBNP Co)
2) Daesung aquamox ju (Daesung microorganism Research Co)
3) CocoShot (Daehan New Pharam Co)
4) Aqua Amoxicillin inj. (Samyang AniPharm Co)
5) AQUA AMOXIN-CARE Inj. (YuniBiotech Co)
6) HD Moxy-F Inj. (Han Dong Co)
7) Aqua Moxamixs Inj. (Eaglevet Co)
8) Amoxa SP inj. for fish (Ewha PharmTek Co)

(C) Amoxicillin (tri)hydrate + Florfenicol by Upper intramuscular injection

1) Daesung Aqua AFJu (Daesung microorganism Research Co)

4. Chemical names and CAS registry number

Amoxicillin sodium(CAS: 34642-77-8), Amoxicillin hydrate (CAS: 61336-70-7)

5. Names and addresses of basic producers

1) Nel biotech Co: 808-15 Ducksan Industrial site, Dusanri, Samjukmun, Ansung, Gyeonggi-Do, Korea (456-882)
2) Dawonchemical Co: # 1402, 14F, aT center 27 GangnamDaero, SeochoGu, Seoul, Korea
3) Woosung Co: 6F, Woosung Building, 1027 Hanbabdaero, DeadeokGu, Daejeon, Korea
4) Jeibisolution Co: 222-15, Bochaeri, Miyangmyun, Ansung, Gyeonggi-Do, Korea (456-843)
5) Komipharm Co: 17 gyeongjero, Jungwangdong, Siheungsi, Gyeonggi-Do, Korea (429-450)
6) Green cross Veterinary products Co: 438, Jungbudaero Giheunggu, Yongin, Gyeonggi-Do, Korea (446-569)
7) Daehan New Pharam Co: 1062-4, Namhyundong, Gwanakgu, Seoul, Korea (151-801)
8) DongbuPharmhannong Co: Nobel building 4F, 15, 78Gil, Taehaeranro, Gangnamgu, Seoul, Korea (135-840)
9) Samu median Co: 632-7, Deungchon-1-dong, Ganseogu, Seoul, Korea
10) Seoul Vet Pharma Co: 164-5, Yongchonri, Mangdongmyeon, Eumsunggun, Chungbukdo, Korea (369-810)
11) KOFAVET special Co: 220, Bongjuro, Sunggaup, Sungbukgu, Chunan city, Chungnamdo, Korea (331-835)
12) Samyang AniPharm Co: 404-5, Kalhyun-dong, Eunpyeong-ku, Seoul, Korea
13) SF Co: 253-16, Wonsiro, Danwongu, Ansan city, Gyeonggi-do, Korea (425-090)
14) WooGene B&G Co: R.No. 1504, Ace Hitech city 1-dpng, Gyeonin-ro 775, Yeongdeungpo-gu, Seoul, Korea (150-972)
15) YuniBiotech Co: 4F, 1489-7, Seocho 3 dong, SeochoGu, Seoul, Korea (137-869)
16) Eaglevet Co: 8F, Eagle Town Bulg, #20, 6-gil Gananru-ro, sungdondgu, Seoul, Korea (133-832)
17) Ewha PharmTek Co: #245-4, Seoam-ri, Tongjin-eup, Gimpo-si, Gyeonggi-do, Korea (415-866)
18) JinWoo Vet.Pharm Co: 229, Hyoryeong-ro, Seocho-gu, Seoul, Korea
19) CharmsinPharm Co: 169-3 Jubukri, Yangjimyeon, CheinGu, Yongin city, Gyeonggi-do, Korea (449-822)
20) HanGukSumVet Co: #802, 8F, E-landtakdong, 2 sevenventurevalley, Pangyo 633 Sampyeongdong, Bundang-gu, Sungnam city, Gyeonggi-do, Korea
21) KBNP Co: Doosan Venture-digm 706, 126-1 Pyeongchon Dongan-Gu, Anyang, Gyeonggi-Do, Korea (431-755)
22) SungWon Co: 15, 183 bungil, Seoamro, Gimpo city, Gyeonggi-do, Korea
23) CTC Bio Co: CTC Bldg, 93, Ogeum-dong, Sonpa-gu, Seoul, Korea (138-858)
24) Han dong Co: #5F, Han dong BLdg, 535 Ogumro, SongpaGu, Seoul, Korea (138-814)

PURPOSE, SCOPE AND RATIONALE

6. Identification of the food safety issue (residue hazard)

7. Assessment against the criteria for the inclusion on the priority list

RISK PROFILE ELEMENTS

8. Justification for use

Prevention and treatment of fish diseases

9. Veterinary use pattern, including information on approved uses if available

1) Amoxicillin hydrate
   - Oral administration (20~40 mg/Kg body weight of fish for 4~7 days)
   - Efficacy: Furunculosis (*Photobacterium damselae* subsp*. piscicida*) in yellow tail

2) Amoxicillin sodium
   - - Upper intramuscular injection (single dose 12.5 or 40 mg/Kg body weight of fish for 1 day)
   - - Efficacy: Streptococcusis (Streptococcus iniae) in olive flounder

3) Amoxicillin (tri)hydrate + Florfenicol
   - - Upper intramuscular injection (single dose 10 mg/Kg body weight of fish for 1 day)
   - - Efficacy: Streptococcusis (Streptococcus iniae) and Edwardsielosis (Edwardsiella tarda) in olive flounder

10. Commodities for which Codex MRLs are required

Fish (ex. yellow tail, flat fish)

RISK ASSESSMENT NEEDS AND QUESTIONS FOR THE RISK ASSESSORS

11. Specific request to risk assessors

AVAILABLE INFORMATION

12. Countries where the veterinary drugs are registered

Member	Name	Species	Tissue	MRL
EU	Amoxicillin	All food producing species (including Fin fish)	Muscle + skin	0.05
Japan	Amoxicillin	Salmon/Eel/Perciform/Other fish	Edible tissue	0.05

13. National/Regional MRLs or any other applicable tolerances

MRLs: 0.05 mg/kg in fish

14. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available

1) Jung soo Seo et al., (2015) Pharmacokinetics of amoxicillin trihydrate in cultured olive flounder (*Paralichthys olivaceus*). JOURNAL OF VETERINARY PHARMACOLOGY AND THERAPEUTICS (*In press*): **Pharmacology**

2) Eun Ji Jeon, Jung soo Seo et al., (2010) Pharmacokinetics of Amoxicillin trihydrate in Cultured Eel *Anguilla japonica* by single oral and intravenous administrations. Journal of Fish Pathology 23: 357-367: **Pharmacology (Written by Korean)**

3) Kwang-Tae Son et al (2011) Residues of Ampicillin and Amoxicillin in Olive Flounder (*Paralichthys olivaceus*) Following Oral Administration. Kor J Fish Aquat Sci 44: 464-469: **residue depletion (Written by Korean)**

4) Chung HS, Kim S, Min WG and Lee HJ. (2006) Muscle tissue distribution level of amoxicillin in olive flounder (*Paralichthys olibaceus*), rockfish (*Sebastes schlegeli*), and red sea bream (*Pagrus major*) following oral administration. J Food Hyg Safety 21, 244-249: **residue depletion & analytical methods (Written by Korean)**

TIMETABLE

15. Date when data could be submitted to JECFA

Proposed date: February 2015

Ampicillin

ADMINISTRATIVE INFORMATION

1. Member(s) submitting the request for inclusion

Republic of Korea

2. Veterinary drug names

Ampicillin sodium, Ampicillin hydrate

3. Trade names

(A) Ampicillin hydrate by oral administration

1) Susanyong-Ampilin 100 (Nel biotech Co)
2) Susnayong Noxsu Ampicin (Green cross Veterinary products Co)
3) PurunBada Ampicin (Green cross Veterinary products Co)
4) Hiampilin (Dawonchemical Co)
5) Aqua ampicin (Daehan New Pharam Co)
6) Amblosin (DongbuPharmhannong Co)
7) B.K Ampicin (BoGuk Co)
8) Susnayong ampicillin-10 suyongsan (Samyang AniPharm Co)
9) Samu Ampicillin powder (Samu median Co)
10) Aqua Ampi powder (Seoul Vet Pharma Co)
11) Susanyong Ampigold (SungWon Co)
12) GD Ampicillin (Woosung Co)
13) Susanyong Ampicillin-10 (WooGene B&G Co)
14) Fish Ampi (YuniBiotech Co)
15) ELTampicillin-200 Susanyong (ELT science Co)
16) Ewha ampicillin (Ewha PharmTek Co)
17) Green Ampicillin 200 (Jeibisolution Co)
18) JinWoo Ampicil 200 (JinWoo Vet.Pharm Co)
19) Chamshin amcillin-200 (CharmsinPharm Co)
20) Aqua ampid powder-200 (Komipharm Co)
21) Vixxol AmpiOne for fish (KOFAVET special Co)
22) Susanyong Sum vet Ampicillinsan (HanGukSumVet Co)
23) Susanyong Ampicillinsan (Han Dong Co)

(B) Ampicillin sodium by Upper intramuscular injection

1) Kampicillin Aqua injection (KBNP Co)
2) Aqua Eagle-Binopen Inj. (Eaglevet Co)

4. Chemical names and CAS registry number

Ampicillin sodium (CAS: 69-52-3), Ampicillin hydrate (CAS: 7177-48-2)

5. Names and addresses of basic producers

1) Nel biotech Co: 808-15 Ducksan Industrial site, Dusanri, Samjukmun, Ansung, Gyeonggi-Do, Korea (456-882)
2) Green cross Veterinary products Co: 438, Jungbudaero Giheunggu, Yongin, Gyeonggi-Do, Korea (446-569)
3) Dawonchemical Co: # 1402, 14F, aT center 27 GangnamDaero, SeochoGu, Seoul, Korea
4) Daehan New Pharam Co: 1062-4, Namhyundong, Gwanakgu, Seoul, Korea (151-801)
5) DongbuPharmhannong Co: Nobel building 4F, 15, 78Gil, Taehaeranro, Gangnamgu, Seoul, Korea (135-840)
6) BoGuk Co: 664-1, Hwangyongri, Bonghwangmyun, Naju city, Chonnamdo, Korea
7) Samyang AniPharm Co: 404-5, Kalhyun-dong, Eunpyeong-ku, Seoul, Korea

8) Samu median Co: 632-7, Deungchon-1-dong, Ganseogu, Seoul, Korea
9) Seoul Vet Pharma Co: 164-5, Yongchonri, Mangdongmyeon, Eumsunggun, Chungbukdo, Korea (369-810)
10) SungWon Co: 15, 183 bungil, Seoamro, Gimpo city, Gyeonggi-do, Korea
11) Woosung Co: 6F, Woosung Building, 1027 Hanbabdaero, DeadeokGu, Daejeon, Korea
12) WooGene B&G Co: R.No. 1504, Ace Hitech city 1-dpng, Gyeonin-ro 775, Yeongdeungpo-gu, Seoul, Korea (150-972)
13) YuniBiotech Co: 4F, 1489-7, Seocho 3 dong, SeochoGu, Seoul, Korea (137-869)
14) ELT science Co: 38 OsongSanmyong 6 ro, OsongUp, ChungwonGun, Chungbukdo, Korea (363-954)
15) Ewha PharmTek Co: #245-4, Seoam-ri, Tongjin-eup, Gimpo-si, Gyeonggi-do, Korea (415-866)
16) Jeibisolution Co: 222-15, Bochaeri, Miyangmyun, Ansung, Gyeonggi-Do, Korea (456-843)
17) JinWoo Vet.Pharm Co: 229, Hyoryeong-ro, Seocho-gu, Seoul, Korea
18) CharmsinPharm Co: 169-3 Jubukri, Yangjimyeon, CheinGu, Yongin city, Gyeonggi-do, Korea (449-822)
19) Komipharm Co: 17 gyeongjero, Jungwangdong, Siheungsi, Gyeonggi-Do, Korea (429-450)
20) KOFAVET special Co: 220, Bongjuro, Sunggaup, Sungbukgu, Chunan city, Chungnamdo, Korea (331-835)
21) HanGukSumVet Co: #802, 8F, E-landtakdong, 2 sevenventurevalley, Pangyo 633 Sampyeongdong, Bundang-gu, Sungnam city, Gyeonggi-do, Korea
22) Han dong Co: #5F, Han dong BLdg, 535 Ogumro, SongpaGu, Seoul, Korea (138-814)
23) KBNP Co: Doosan Venture-digm 706, 126-1 Pyeongchon Dongan-Gu, Anyang, Gyeonggi-Do, Korea (431-755)
24) Eaglevet Co: 8F, Eagle Town Bulg, #20, 6-gil Gananru-ro, sungdondgu, Seoul, Korea (133-832)

PURPOSE, SCOPE AND RATIONALE

6. Identification of the food safety issue (residue hazard)

7. Assessment against the criteria for the inclusion on the priority list

RISK PROFILE ELEMENTS

8. Justification for use

Prevention and treatment of fish disease

9. Veterinary use pattern, including information on approved uses if available

1) Ampicillin hydrate
   - oral administration (5~20 mg/Kg body weight of fish for 5 days)
   - Efficacy: Furunculosis (*Photobacterium damselae* subsp*. piscicida*) in yellow tail
2) Ampicillin sodium
   - Upper intramuscular injection (single dose 20 mg/Kg body weight of fish for 1 days)

     Efficacy: Streptococcusis (Streptococcus iniae or S. parauberis) in olive flounder

10. Commodities for which Codex MRLs are required

Fish (Flat fish, yellow tail)

RISK ASSESSMENT NEEDS AND QUESTIONS FOR THE RISK ASSESSORS

11. Specific request to risk assessors

AVAILABLE INFORMATION1

12. Countries where the veterinary drugs are registered

Member	Name	Species	Tissue	MRL
EU	Ampicillin	All food producing species (including Fin fish)	Muscle + skin	0.05
Japan	Ampicillin	Salmon/Eel/Perciform/Other fish	Edible tissue	0.05

13. National/Regional MRLs or any other applicable tolerances

MRLs: 0.05 mg/kg in fish

14. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available

1) Jung S.H et al., (2012) Residues of ampicillin in blood of cultured olive flounder by oral, injection and dipping administration. Journal of Fish Pathology 25: 211-219: **Pharmacology (Written by Korean)**

2) Kwang-Tae Son et al., (2011) Residues of Ampicillin and Amoxicillin in Olive Flounder (*Paralichthys olivaceus*) Following Oral Administration. Kor J Fish Aquat Sci 44: 464-469: **residue depletion (Written by Korean)**

TIMETABLE

15. Date when data could be submitted to JECFA

Proposed date: February 2015

UNITED STATES OF AMERICA

Administrative Information

1. Member(s) submitting the request for inclusion

United States of America

2. Veterinary drug names

Ivermectin

3. Trade names

Multiple Properietary and Generic Brands globally. (e.g.), Ivomec

4. Chemical names and CAS registry number

Ivermectin is a macrocyclic lactone class and is a mixture of 22,23-dihydroavermectin B1a (H_2 B_{1a}) and 22,23-dihydroavermectin B1b (H_2 B_{1b})

Chemical Abstracts Service (CAS) registry number for Ivermectin: 70288-86-7

5. Names and addresses of basic producers

Multiple producers globally. Sponsor – Merial Inc. 3239 Satellite Blvd, Duluth, GA 30096.

Purpose, Scope and Rationale

6. Identification of the food safety issue (residue hazard)

Ivermectin is a broad spectrum antiparasitic drug which is registered globally for use against nematode and anthropod parasites in food producing animals. Recently available information could allow a re-evaluation of the current CODEX ADI.

7. Assessment against the criteria for the inclusion on the priority list

Ivermectin has been previously reviewed by the CODEX committee at its thirty-sixth, fortieth, fifty-eighth and seventy-fifth meetings. Ivermectin is at Step 3 for establishment of an MRL for bovine muscle and is currently on the provisional agenda for the 22nd CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS (CCVRDF) for discussion of comments on proposed draft MRL's for bovine muscle.

Risk Profile Elements

8. Justification for use

Well-established broad spectrum antiparasitic drug that has in use for more than 30 years (since 1981) for veterinary use and for about 25 years (since 1987) for human use.

9. Veterinary use pattern, including information on approved uses if available

Target species: Cattle, Sheep, Pigs, Horses, Deer, Other

Major indications: Treatment and control of endo- and ectoparasites

Dose Regimen for animals: Depending on the route of administration and species a dose range 100 - 500 µg ivermectin/kg bodyweight (bw) is used.

10. Commodities for which Codex MRLs are required

Bovine MRL's

Risk Assessment Needs and Questions for Risk Assessors

11. Specific request to risk assessors

a. Reevaluate the ADI based on more recently available information.

b. Reevaluate the MRL based on the revised ADI and other pertinent information.

Available information

12. Countries where the veterinary drugs are registered

Ivermectin products are registered for veterinary use broadly around the world.

13. National/Regional MRLs or any other applicable tolerances

EU: EU (COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE EMEA/MRL/915/04-FINAL November 2004) established an ADI of 10 µg/kg bw/day.

Annex to Commission Regulation (EU) No. 37/2010: Ivermectin MRL's for all Food-Producing Species

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Ivermectin	22,23-Dihydro-avermectin B1a	All mammalian food producing species	30 µg/kg 100 µg/kg 100 µg/kg 30 µg/kg 1250 µg/kg	Muscle Fat Liver Kidney Injection Site Residue Reference Value	For porcine species the fat MRL relates to 'skin and fat in natural proportions' Not for use in animals from which milk is produced for human consumption	Antiparasitic agents/Agents acting against endo and ectoparasites

US: Federal Register /Vol. 79, No. 208 /Tuesday, October 28, 2014 /Rules and Regulations published the update to the Title 21, Code of Federal Regulation Part § 556.344 for Ivermectin.

(a) Acceptable Daily Intake (ADI): The ADI for total residues of ivermectin is 5 micrograms per kilogram of body weight per day.

(b) Tolerances (1) Liver: A tolerance is established for 22,23-dihydroavermectin B1a (marker residue) in liver (target tissue) of Cattle as 1.6 ppm (1600 µg/kg) and (2) Muscle: A tolerance is established for 22,23-dihydroavermectin B1a (marker residue) in muscle of Cattle as 650 parts per billion (650 µg/kg).

14. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methods) available.

a. Justification to support revised ADI based on:

   1. Toxicity in dogs

   2. Human tolerance study and other use information in humans

b. Residue Depletion Study

Timetable

15. Date when data could be submitted to JECFA

2015