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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Viale delle Terme di Caracalla 00153 ROME Tel: 39 06 57051 www.codexalimentarius.net Email: codex@fao.org Facsimile: 39 06 5705 4593

Agenda Item 5 (b) **CX/RVDF 09/18/5 Add.1**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Eighteenth Session

Natal, Brazil

11-15 May 2009

PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS

(at Step 3 of the Procedure)

Comments submitted by Iran, Philippines, United States of America, Uruguay and International Federation for Animal Health (IFAH)

AVILAMYCIN

IRAN

Iran supports the proposed MRLs for Avilamycin.

PHILIPPINES

Phillipines recommends that the MRLs for Avilamycin be retained at Step 3

Proposed maximum residue limits (MRLs) in ug/kg for pigs, chicken, turkey and rabbits:

Skin/fat 100

Kidney 200

Liver 300

Muscle 50

Rationale **:**

Registration: Avilamycin is approved by the Philippines Bureau of Animal Industry for antibacterial / anti-infective agent since 1994.

Approved Indications and Dosages:

-Broilers: For the improvement of average daily gain and feed conversion efficiency and for the prevention and control of Necrotic Enteritis caused by *Clostridium perfringens*. Dosage: 2.5 to 15ppm

-Pigs: For the improvement of average daily gain and feed conversion efficiency and as aid in the control of post weaning diarrhea associated with *Escherichia coli*. Dosage: 10-40ppm

Pharmacokinetics:

Blood, serum or plasma concentrations in various species following oral doses: limits of detection (e.g., <0.04 to <0.1 µg/mL) (6) (West et al., 1982). Classic pharmacokinetic data are not available as the antibiotic is not present in plasma at concentrations sufficient for kinetic analysis. lower levels of quantitation necessary for kinetic analysis would be well below the toxicologically relevant concentration and thus would not be relevant to human food safety.

Absorption:

- Poorly absorbed when administered orally

Distribution:

-Summary of the radioactive tissue residues (ug/g of total residues) at zero day withdrawal in swine and chicken consuming avilamycin in the feed

Table 2 Summary of the radioactive tissue residues[a] (µg/g of total residues) at zero day withdrawal in swine consuming avilamycin in the feed

	Study Number [dose of avilamycin in feed]			
	ABC-0266 (12) [60 mg/kg][b] 5 days	ABC-0287 (13) [80 mg/kg][b] 10 days	ABC-0308 (14) [80 mg/kg][b] 7 days	ABC-0360 (15)[a] [60 mg/kg][b] 14 days
Label position:	[DIA-^{14}C]	[DIA-^{14}C]	[DIA-^{14}C]	[U-^{14}C]
Liver	0.13	0.22	0.15	0.66
Kidney	0.08	0.1	0.08	0.34
Muscle	<0.01[c]	0.016	<0.024[c]	0.14
Fat	0.03	0.12	0.07	0.55

[a] Radioactive tissue residues are higher in study ABC-0360 (15) than the other three studies because the radioactivity was more uniformly distributed throughout the molecule. See detailed discussion in section 2.2.3 Metabolism.
[b] Microbiological equivalents of [^{14}C]avilamycin
[c] Assay limit of detection

Table 3 Summary of the radioactive tissue residues (µg/g of total residues) at zero day withdrawal in chickens consuming avilamycin in the feed

	Study Number [dose of avilamycin in feed]	
	ABC-0329 (16) [15 mg/kg][a]	T4E969602 (17) [30 mg/kg][a]
Label position:	[DIA-^{14}C]	[U-^{14}C]
Liver	0.022	0.08
Kidney	<0.024 [b]	0.07
Muscle	<0.008 [b]	<0.04 [b]
Fat	0.022 [c]	0.03
Egg (whole)	--	0.12 [d]

[a] Microbiological equivalents of [^{14}C]avilamycin
[b] Assay limit of detection
[c] One of four individuals < LOD (0.009 µg/g was used to calculate mean)
[d] Calculated from LOD of albumin and radioactive yolk residue:
(0.07 µg/g X 0.67) + (0.22 µg/g X 0.33)

No distribution data for avilamycin in turkeys and rabbits.

Excretion

- Primarily excreted in feces when administered orally to swine or chickens

Dalidowicz J E, Thomson T C, and Herberg R J (1983) 14C Avilamycin Balance-Excretion Study in Swine Study ABC-0229 (Dalidowicz, et al., 1983).

- Two crossbred gilts received 0.9 kg of feed containing unlabeled avilamycin at 60 mg/kg activity twice a day for 7 days
- After 7 days, gave each gilt 120 mg of radiolabeled ^{14}C-Avilamycin
- The bulk was excreted on the first 4 days with over 91% coming on day 2 and 3.
- 93.4% of the residue in feces and 4.54% in the urine
- Feces is the main route of excretion
- Dalidowicz et al 1984. A balance-excretion study in chickens (11) (): broiler chickens
- (2M/2F) were administered non-radiolabeled avilamycin at 20 mg of microbiological activity per kg in the feed.
- After 7 days administration to approximate steady state, a single bolus dose of 4 mg of [U-14C]avilamycin was administered and excreta was collected at 24-hr intervals for 13 days.

- During the collection period, the birds excreted 92.8%, 99.2%, 96.6% and 84.4% of the dose, respectively. An average of 90% of the radioactivity was excreted within the first 6 days.

(Analytical Method)

- -Method Number AM-AA-CA-R056-AB-755, Microbiological Assay For Avilamycin In Whole Blood, Serum, Or Feces. Eli Lilly and Company, Greenfield, Indiana, USA (Eli Lilly and Company, Method Number AM-AA-CA-R056-AB-755)
- -Method Number AM-AA-CA-R050-AB-755, Gas Chromatographic Determination Of Avilamycin And Its Metabolites In Animal Blood And Feces. Eli Lilly and Company, Greenfield, Indiana, USA (Eli Lilly and Company, Method Number AM-AA-CA-R050-AB-755)
- -Method Number AM-AA-CA-R075-AB-755, Bioautographic Detection Of Avilamycin Residues In Swine And Broiler Tissues. Eli Lilly and Company, Greenfield, Indiana, USA (Eli Lilly and Company, Method Number AM-AA-CA-R075-AB-755)
- -Gas Chromatographic Determination Of Avilamycin And Its Metabolites Containing Method Number AM-AA-CA-R093-AA-755, Dichloro-Isoeverninic Acid In Animal Tissues. Eli Lilly and Company, Greenfield, Indiana, USA (Eli Lilly and Company, Method Number AM-AA-CA-R093-AA-755)
- -Eichmeier, L.S. (2006) Report No. 49783, "Validation of an HPLC-MS/MS Method for the Determination of Avilamycin in Chicken Liver, Kidney, Muscle, and Fat/Skin" .ABC Laboratories, Inc., Columbia, MO, USA (ABC Method 49783-MI). (Eichmeier, 2006a)
- -Eichmeier, L.S. (2006) Report No. 49784, "Validation of an HPLC-MS/MS Method for the Determination of Avilamycin in Swine Liver, Kidney, Muscle, and Fat/Skin" .ABC Laboratories, Inc., Columbia, MO, USA (ABC Method 49784-MI-01). (Eichmeier, 2006b)

Tissue Residue Studies

Summary of the microbiologically active tissue residues (µg/g of total residues) at zero day withdrawal in swine consuming avilamycin in the feed

	Study Number [dose of avilamycin in feed]				
	Maurer, et al. [100 mg/kg]	I-EWD-83-09 [40 mg/kg]	I-EWD-83-10 [100 mg/kg]	61-118 [400 mg/kg]	86-133 [400 mg/kg]
Liver	0.15	<0.05[a]	<0.05[a]	<0.025[a]	<0.025[a]
Kidney	<0.09[a]	<0.05	<0.05	<0.025	<0.025
Muscle	<0.07[a]	<0.05	<0.05	<0.025	<0.025
Fat	<0.08[a]	<0.05	<0.05	<0.025	<0.025

[a] Assay limit of detection

Summary of the tissue residues (µg/g of total residues) at zero day withdrawal in chickens consuming avilamycin in the feed

	Study Number [dose of avilamycin in feed]			
	T4EUA9501[a] [15 mg/kg]	I-EWD-83-11[b] [20 mg/kg] 56 days	86-134[b] [200 mg/kg] 56 days	61-142[b] [200 mg/kg] 56 days
Liver	--	<0.05[c]	< 0.025[c]	< 0.025[c]
Kidney	--	<0.05	< 0.025	< 0.025
Muscle	--	<0.05	< 0.025	< 0.025
Fat	--	<0.05	< 0.025	< 0.025
Egg (whole)	<0.02[c]	--	--	--

[a] Analysis by HPLC with UV detection for avilamycin A; eggs only.
[b] Micobiological assay
[c] Assay limit of detection

Withdrawal period

The residues in edible tissues are low or not detectable in swine and chicken at zero time (6hr) withdrawal.

Toxicological Residue Risk Assessment

Toxicological Acceptable Daily Intake

- - The NOELs for avilamycin in the two-year rat study were 110 mg/kg/day for males and 128 mg/kg/day for females. The lowest NOEL dose was used to calculate the ADI.
- -The toxicological ADI for avilamycin was proposed to be 66 mg per day (1.1 mg/kg bw/day). (Expert report on the Safety File for Avilamycin)

Consumption of Residues from swine tissues (Toxicological ADI)

Food Basket Consumption of Potential Avilamycin Residues Following Consumption of Swine Products Based on Total Radioactive Residues

Tissue	Daily Consumption (g)	Total Avilamycin Intake (based on radioactivity) (mg/kg)	(mg)
Liver	100	0.66	0.066
Kidney	50	0.34	0.017
Muscle	300	0.14	0.042
Fat	50	0.55	0.028
Total			**0.153 mg**

At zero withdrawal, the maximum amount of residue is 0.153 mg (based on radioactivity), which is equivalent to: (0.153 mg/day/66 mg/day) x 100% = 0.23% of the Toxicological ADI

Therefore, the use of Avilamycin in swine at zero withdrawal does not pose a toxicological hazard to consumers of swine meat.

Consumption of residues from chicken tissues (Toxocological ADI)

Chicken: 30mg/kg avilamycine dosage in feed (Sweeney et al, 1996)

Food Basket Consumption of Potential Avilamycin Residues Following Consumption of Chicken Products Based on Total Radioactive Residues

Tissue	Daily Consumption (g)	Total Avilamycin Intake (based on radioactivity) (mg/kg)	(mg)
Liver	100	0.08	0.008
Kidney	10	0.07	0.0007
Muscle	300	0.04[a]	0.012
Fat	90	0.03	0.0027
Egg Albumin	67[b]	0.07[a]	0.005
Egg Yolk	33[b]	0.22	0.007
Total			**0.035 mg**

[a] Assay limit of detection; [b] albumin:yolk = 2:1, consumption factor = 100 g

At zero withdrawal, the maximum amount of residue is 0.035 mg (based on radioactivity), which is equivalent to: (0.035 mg/day/66 mg/day) x 100% = 0.05% of the Toxicological ADI

Therefore, the use of Avilamycin in poultry at zero withdrawal does not pose a toxicological hazard to consumers of poultry meat.

Microbiological Residue Risk Assessment

Microbiological Acceptable Daily Intake (ADI)

A microbiological ADI of 55.7 µg/kg bw/day has been proposed by Elanco based on a study of human gut flora using the guideline calculation (CVMP/234/01-FINAL; see Safety File).

The ADI for a typical human of 60 kg body weight is 0.557 mg/kg/day X 60 kg = 3.34 mg/day. (Expert report on the Safety File for Avilamycin)

Consumption of residues from swine tissues (Microbiological ADI)

Exaggerated dose of 400 mg/kg avilamycin in feed fed to swine, Morimoto et al., 1986a, Asanuma et al., 1987a

Food Basket Consumption of Potential Avilamycin Residues Following Consumption of Swine Products Based on Microbiological Residues

Tissue	Daily Consumption (g)	Total Avilamycin Intake (mg/kg)	(mg)
Liver	100	0.025[a]	0.0025
Kidney	50	0.025[a]	0.00125
Muscle	300	0.025[a]	0.0075
Fat	50	0.025[a]	0.00125
Total			**0.0125 mg**

[a] Assay limit of detection

(0.0125 mg/day/3.34 mg/day) x 100% = 0.37% of the Microbiological ADI

Therefore, the use of Avilamycin in swine at zero withdrawal does not pose a hazard to consumers of swine meat, nor a risk of developing antimicrobial resistance.

Exaggerated dose of 200 mg/kg avilamycin in feed fed to chickens, Morimoto et al., 1986a, Asanuma et al., 1987a

Food Basket Consumption of Potential Avilamycin Residues Following Consumption of Chicken Products Based on Microbiological Residues

Tissue	Daily Consumption (g)	Total Avilamycin Intake (mg/kg)	(mg)
Liver	100	0.025[a]	0.0025
Kidney	10	0.025[a]	0.00025
Muscle	300	0.025[a]	0.0075
Fat	90	0.025[a]	0.00225
Egg Albumin	67	0.07[a,b]	0.0047
Egg Yolk	33	0.22[b]	0.0073
Total			**0.0245 mg**

[a] Assay limit of detection; [b]radioactive residue

(0.0245 mg/day/3.34 mg/day) x 100% = 0.7% of the Microbiological ADI

Therefore, the use of Avilamycin in broiler chickens at zero withdrawal does not pose a hazard to consumers of chicken meat, nor a risk of developing antimicrobial resistance.

UNITED STATES OF AMERICA

The United States supports the proposed draft MRLs for avilamycin for advancement to Step 5.

URUGUAY

Uruguay has no comments on avilamycin ; it is not registered in our country.

IFAH

IFAH supports the proposed draft MRLs for avilamycin for advancement to Step 5.

DEXAMETHASONE (GLUCOCORTICOSTEROID)

IRAN

Iran supports the proposed MRLs for dexamethasone.

PHILIPPINES

Philippines suggests the following MRLs for dexamethasone:

Proposed Maximum Residue Limits for cattle, pigs and horses (ug/kg):

Muscle: 0.5ug/kg

Liver: 2.0 ug/kg

Kidney: 0.5ug/kg

Cow's milk: 0.3 ug/L

Rationale: Due to many adverse effects of dexamethasone to humans, observed effects on animals and interaction of dexamethasone to other drugs existing data should be further reviewed and evaluated for the safety of the consumers.

UNITED STATES OF AMERICA

The United States supports the proposed draft MRLs for dexamethasone for advancement to Step 5.

URUGUAY

Uruguay supports the proposed draft MRLs for dexamethasone for advancement to Step 5.

IFAH

IFAH supports the proposed draft MRLs for dexamethasone for advancement to Step 5.

MONENSIN (ANTIMICROBIAL AGENT AND PRODUCTION AID)

IRAN

Iran supports the proposed MRLs for monesin.

PHILIPPINES

Philippines supports the recommended maximum residue limits (MRLs) by JECFA in liver of cattle 10 ug/kg ; Milk 2ug/kg.

Philippines proposes 50ug/kg MRLs for cattle, sheep, goats, chicken, turkey and quail (fat, kidney, liver (except in cattle), muscle)

Rationale: We support the MRLs provided by Canadian Food and Drug Regulations on Adulteration of Food (Item No. M.1) ref: http://laws.justice.gc.ca/en/showdoc/cr/C>R>C.-c.870/bo-ga:1_B-gb:1_15//en accessed 7/102007

UNITED STATES OF AMERICA

The United States does not support the proposed draft MRLs for monensin. The draft MRLs for monensin appears inconsistent with the data provided and those established by other countries. Therefore, we propose that the draft MRLs be returned to JECFA.

Rationale: The proposed draft MRLs for monensin do not reflect all current approved uses as there are some countries that have approved two formulations of monensin that can be used concurrently. These approved uses result in residues that are above the proposed draft MRLs but within safe tolerances. The United States proposes that the JECFA reevaluate the MRLs for monensin taking into consideration these labelled uses.

URUGUAY

Uruguay supports the proposed draft MRLs for Monensin advancement to Step 5.

IFAH

IFAH does not support the advancement of MRLs for monensin and recommend that it be returned to JECFA for re-evaluation. The recommended MRLs for monensin appear to be inconsistent with the data provided, and those established by other countries.

Rationale: The MRLs for monensin could inhibit the facilitation of trade of meat and poultry products in that they are below the MRLs already established by other country regulatory authorities.

Current approvals in countries affirm that two formulations of monensin can be used concurrently, thus resulting in higher levels of monensin than the current Good Veterinary Practices (GVP) would have estimated. As these approved label uses are within safe tolerances, JECFA and CCRVDF should take these approved labels into account.

The unnecessarily low MRLs for monensin is the result of the current practice by JECFA and CCRVDF of applying GVP. As noted in the US Delegation's comments, the use of GVP can result in significant problems. Monensin is a good examples of why the current procedures for determining MRLs should be re-evaluated.

NARASIN (ANTIMICROBIAL AGENT AND PRODUCTION AID)

IRAN

Iran supports the proposed MRLs for narasin.

UNITED STATES OF AMERICA

The United States does not support the proposed draft MRLs for narasin. The draft MRLs for narasin appear inconsistent with the data provided and those established by other countries. Therefore, we propose that the draft MRLs be returned to JECFA.

Rationale : The proposed draft MRLs for narasin are lower than the limit of quantification (LOQ) for the narasin analytical method. The United States proposes that the MRLs be raised to be consistent with the current analytical method as to allow developing countries to implement the standard and thereby continue to ensure the safety of food.

URUGUAY

Uruguay supports the proposed draft MRLs for narasin to advancement to Step 5.

PHILIPPINES

Philippines supports the proposed draft MRLs for narasin.

IFAH

IFAH does not support the advancement of MRLs for narasin and recommend they be returned to JECFA for re-evaluation. The recommended MRLs for narasin appear to be inconsistent with the data provided, and those established by other countries.

Rationale : The MRLs for narasin could inhibit the facilitation of trade of meat and poultry products in that they are below the MRLs already established by other country regulatory authorities.

The MRLs proposed for narasin are at levels which are below the limit of quantification (LOQ) for the narasin analytical method. Appropriately raising the MRLs to be consistent with the current analytical method would allow developing countries to implement the standard, thereby continuing to ensure the safety of food.

The unnecessarily low MRLs for narasin is the result of the current practice by JECFA and CCRVDF of applying GVP. As noted in the US Delegation's comments, the use of GVP can result in significant problems. Narasin is a good examples of why the current procedures for determining MRLs should be re-evaluated.

TILMICOSIN (ANTIMICROBIAL AGENT)

IRAN

Iran supports the proposed MRLs for tilmicosin.

PHILIPPINES

Philippines supports the 47th JECFA Meeting's recommendation for MRLs of chicken and turkey.

The Philippines propose an MRL for egg: 300ug/kg.

Rationale: Pharmacokinetics

Summary of tilmicosin concentrations in lung, air sac and plasma following continuous medication for up to three days at 75 mg /L

Hours after treatment	Mean Tilmicosin concentration in lung tissue (mg/kg)	Tilmicosin concentration in pooled airsac tissue (mg/kg)	Mean Tilmicosin concentration in plasma (µg/ml)
6	0.63	0.30	<0.06
12	0.77	0.52	<0.07
24	0.73	0.89	<0.05
36	1.35	1.79	<0.07
48	2.30	3.29	NA*
72	1.53	2.38	<0.09
84	1.67	3.10	<0.10
120	0.87	2.86	<0.07

UNITED STATES OF AMERICA

The United States supports the proposed draft MRLs for tilmicosin for advancement to Step 5.

URUGUAY

Uruguay has no comments on Tilmicosin ; it is not registered for internal use in birds.

IFAH

IFAH supports the supports the proposed draft MRLs for tilmicosin for advancement to Step 5.

TRICLABENDAZOLE (ANTHELMINTIC)

IRAN

Iran supports the proposed MRLs for triclabendazole.

PHILIPPINES

The Philippines propose the following MRLs for cattle:

Proposed the maximum residue limits (MRLs) for cattle:

Muscle: 275ug/kg

Liver: 600 ug/kg

Kidney: 375 ug/kg

Fat: 200 ug/kg

Rationale : The lower MRLs could pose trade obstacles which contradicts one of the objectives of setting food safety with worldwide validity.)

The product Triclabendazole is currently registered with the local authority in the Philippines under the brand, FASINEX 10% and is being sold in the market at 10% concentration in drench suspension. It is suggested therefore that the following MRLs should be considered: Muscle: 275 ug/kg, Liver 600 ug/kg, Kidney: 375 ug/kg, Fat: 200 ug/kg. These values are compatible with the ADI and less prone to pose trade obstacles at the same time. We request that the matter is referred back to JECFA for reassessment considering the low bioavailability of Triclabendazole residues which is scientifically acceptable way to increase the MRLs to levels more in harmony with MRLs set by other scientific organizations. Such scientifically justifiably increased MRLs would be more likely to facilitate trade.

UNITED STATES OF AMERICA

The United States supports the proposed draft MRLs for triclabendazole for advancement to Step 5.

IFAH

IFAH supports the proposed draft MRLs for triclabendazole for advancement to Step 5.

TYLOSIN (ANTIMICROBIAL AGENT)

IRAN

Iran supports the proposed MRLs for Tylosin.

PHILIPPINES

The Philippines support the MRLs as suggested by JECFA except for milk which is 50ug/kg and egg which is 200 ug/kg.

UNITED STATES OF AMERICA

The United States supports the proposed draft MRLs for Tylosin for advancement to Step 5.

URUGUAY

Uruguay supports the proposed draft MRLs for Tylosin advancement to Step 5.

IFAH

IFAH supports the proposed draft MRLs for tylosin for advancement to Step 5.