CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Items 4, 6(c) **RVDF/22 CRD/27**

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

COMMENTS OF CANADA

Agenda Item 4 Matters of Interest arising from FAO/WHO and from the 78th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

Canada would like to suggest that the following Risk Management Recommendations for Gentian Violet be considered by the Committee as a result of the conclusions made at the 78th JECFA meeting on this compound. These recommendations could be advanced following the Codex step process for eventual adoption by the Commission.

Gentian Violet:

JECFA Assessment:

The Committee concluded that it is inappropriate to set an ADI for gentian violet because it is genotoxic and carcinogenic.

Risk Management Recommendations:

In view of the JECFA conclusions on the available scientific information, there is no safe level of residues of gentian violet or its metabolites in food that represents an acceptable risk to consumers. For this reason, competent authorities should prevent residues of gentian violet and its metabolites in food.

Agenda item 6 (c) Proposed draft MRLs for derquantel, emamectin benzoate, ivermectin, lasalocid sodium and monepantel, at Step3

Canada highly appreciates the scientific advice that the JECFA provides to the work of CCRVDF, and supports the establishment of Codex MRLs based on JECFA's recommendations. Regarding the draft lasalocid MRLs being discussed at step 3, Canada would like to take this opportunity to raise the following scientific points for further consideration by JECFA.

1. The MRLs proposed for this compound were calculated based on the estimated daily intake (EDI) approach. Canada had earlier expressed the concern that there would be limitations with using the EDI approach when residue depletion data are highly variable. In the case for lasalocid residues in chicken tissues (see Table 7.5 of the monograph) the standard deviations of residues in each tissue on 1-day withdrawal period (WP) (time for which exposure estimates were evaluated) were much higher than the mean of the residues (i.e., the coefficient of variation was > 100%). Mean and standard deviations of lasalocid A residues at 1-day WP were respectively, 65 ppb and 103 ppb in muscle, 244 ppb and 329 ppb in liver, 128 ppb and 194 ppb in kidney, and 106 ppb and 165 ppb in skin/fat of chickens. Given the highly variable nature of the data used to derive the MRLs, Canada considers that this approach may not be robust enough for the establishment of lasalocid MRLs in order to ensure safety to consumers.
2. JECFA monograph indicates that the residue data from 1-day WP was used to derive the proposed MRLs. However, marker to total residue (MR:TR) ratios based on data for 0-day WP were used instead. There is significant reduction in MR:TR between the 0-day and 1-day WP (see Appendix below). After 1-day WP, the MR:TR remains fairly stable. Hence, the MR:TR ratio at 0-day would likely under-estimate the total exposure. Canada therefore considers that MR:TR based on 1-day WP of <25% for muscle, 8.8% for liver, 14.2% for kidney and 29.2% for skin/fat (see Table 7.2 of the monograph) should be used along with the residue depletion data in the exposure assessment.

3. When the data are insufficient or of quality not suitable for the EDI approach, the JECFA has historically used the theoretical maximum daily intake (TMDI) approach to establish MRLs. Based on our calculation using the same data but using the TMDI approach, if the exposure was estimated using the proposed MRLs and the marker to total residue ratios at 1-day WP, the daily human exposure to lasalocid residues would be 2157.6 µg per person which is 7 times higher than the ADI value of 300 µg per person (see Table 6 of Appendix for detailed calculation).

4. While Canada understands that the new dietary exposure assessment approach piloted by the JECFA in its 78th meeting is still being verified, the global estimate of chronic dietary exposure (GECDE) using the MR:TR on 1-day WP for lasalocid would have exceeded the ADI. The GECDE represents 92% of ADI for adults, 168% of ADI for children and 149% of ADI for infants (see Appendix for calculations). JECFA's conclusion that the GECDE is below the ADI was because of considering the MR:TR for 0-day WP which we believe underestimates the exposure. Given that 1-day WP residue data does not support the safety to consumers based on GECDE approach, perhaps the residue data from 2-day WP would have been ideal to establish MRLs for this compound. The 95th percentile (upper 95% CI) of residue data at 2-day WP would have yielded the MRLs of 100 ppb in muscle, 500 ppb in liver, 250 ppb in kidney and 200 ppb in skin and fat (see Appendix, Table 7).

5. Canada considers that the proposed MRLs may not be consistent with the JECFA's practice of setting MRLs as low as possible if supported by the good veterinary practices established by member countries. Based on the data provided, total radioactive residues in muscle at 0-day and 1-day WP were 80 ppb and 20 ppb, respectively (Table 7.2 of the monograph), and lasalocid A residue in muscle at 1-day WP was 65 ppb (Table 7.5 of the monograph). So, the proposed MRLs of 400 ppb in muscle, for example, may not be consistent with this practice.

Conclusion:

In summary, although the proposed MRLs are based on one of the approaches that JECFA uses, given the limitations of the EDI approach (with highly variable data), Canada is concerned that the proposed MRLs might expose consumers to residues of lasalocid that are higher than the ADI. Therefore, Canada would recommend that the CCRVDF hold the MRLs for lasalocid at Step 3 of the Codex procedure, and request JECFA to re-evaluate the proposed MRLs.

Lasalocid MRLs in Eggs:

JECFA Conclusion: "As the compound is not registered for use in laying hens, according to the sponsor, it is not appropriate to recommend MRLs for eggs."

Canada would suggest that CCRVDF request JECFA to re-evaluate lasalocid data in eggs to recommend appropriate risk management recommendations to ensure food safety based on unintended exposure of this compound to laying hens. A number of countries have established their own risk management decisions in form of Action levels/MRLs however, given the international trade situation with this commodity, this Committee may benefit from having lasalocid values in eggs as international standard.

Appendix

A. Pivotal radiolabelled study data in chickens reviewed by the JECFA

Table 1. Concentration (ppb) of total residues and marker residue in chicken tissues dosed with 125 mg [^{14}C]lasalocid sodium/kg bw for 7 days (Source: Table 7.2 of the monograph)

WP (h)	Kidney			Liver			Muscle			Skin with fat		
	TRR	MR	MR:TR	TRR	MR	MR:TR	TRR	MR	MR:TR	TRR	MR	MR:TR
0	395	122	**0.309** (0.406)*	1223	234	**0.191** (0.224)*	80	41	**0.513** (0.552)*	432	208	**0.481** (0.518)*
24	172	<24.5	0.142	838	73.9	**0.088** (0.086)*	20	<LOD	**<0.25**** (NA)	112	<32.7	**0.292** (0.283)*
72	97	<21.6	**0.223** (0.27)*	558	49.7	**0.089** (0.095)	15	<LOD	NA	70	<22.9	**0.327** (0.339)

*MR:TR calculated based on the real value presented are in bold. The values presented by the JECFA are shown in parentheses (not sure how they were determined). Only one MR:TR is presented if the values calculated based on data agrees with the MR:TR presented in Table 7.2 of the monograph.

**If LOD of 5 ppb is used for MR:TR, the ratio will be less than 25%

Comments: There is significant decrease in MR:TR between 0-day WP and 1-day WP, which then stabilizes. Hence, for the exposure assessment based on residue data on 1-day or 2-day WP, the MR:TR derived at 1-day WP should be used.

B. Pivotal cold residue depletion study data reviewed by the JECFA

Table 2. Mean concentration (ppb) of lasalocid A in chicken tissues treated with lasalocid sodium in feed at 130 mg/kg for 42 days (Source: Table 7.5 of the monograph)

Withdrawal period	Mean concentration of lasalocid A (µg/kg)			
	Muscle	Kidney	Liver	Skin-with-fat
0-day	447 ± 144	1050 ± 339	1840 ± 385	1040 ± 282
1-day	65 ± 103	128 ± 194	244 ± 329	106 ± 165
2-day	23 ± 23	61 ± 70	138 ± 131	37 ± 54
3-day	8.4 ± 2.7	26 ± 11	72 ± 56	10 ± 3.8

Comments: The residue data, particularly those at 1- and 2-day WP, are highly variable.

Table 3. Median concentration (ppb) of lasalocid A residues in chicken tissues treated with lasalocid sodium in feed at 130 mg/kg for 42 days (Source Table 7.10 of the monograph)

Tissue	Median residue concentration (ppb)	
	0-day WP	1-day WP
Liver	1705.0	123.9
Kidney	867.3	50.0
Muscle	401.2	25.0
Skin / fat	1017.1	41.7

C. Exposure Assessment

Estimated daily intake (EDI) approach:

Table 4. Estimated daily intake (µg/person) for lasalocid residues

Tissue	Food basket (kg)	0-day WP			1-day WP		
		Median residue ppb	MR:TR	EDI (µg)	Median residue ppb	MR:TR	EDI (µg)
Liver	0.10	1705.0	0.191	892.7	123.9	0.088	140.8
Kidney	0.05	867.3	0.309	140.3	50.0	0.142	17.6
Muscle	0.30	401.2	0.513	234.6	25.0	0.250	30.0
Skin/fat	0.05	1017.1	0.481	105.7	41.7	0.292	7.1
			Total intake	**1373.3**			**195.5**
			ADI (µg/person)	**300**			
			EDI as % of ADI	**458%**			**65.2%**

When the MR:TR for corresponding days as calculated in Table 1 above are used, the EDI will be 1373.3 µg per person on 0-day WP which represents 458% of the ADI, and 195.5 µg per person on 1-day WP which represents 65.2% of the ADI. The values derived by the Committee are different than those estimated above because of:

1. Use of different MR:TR on 0-day WP than those supported by data presented in the same Table (see Table 1 above),
2. MR:TR from 0-day WP used for estimating the exposure, when the residue data from 1-day WP were used.

However, despite these differences, 1-day WP seems to be the appropriate time for calculating MRLs based on the EDI approach. Please note that the exposure assessment does not change significantly even if the MR:TR of 51.3%, based on 0-day WP, is used for muscle.

Dietary Exposure Assessment approach:

The 75th JECFA has proposed a new dietary exposure assessment approach that utilizes both the GECDE and the global estimate of acute dietary exposure (GEADE) to assess the safety to the consumers from residues of veterinary drugs. This method was piloted by the 78th JECFA. The JECFA used the residue data from 1-day WP, but the MR:TR of 0-day WP, to calculate the GECDE and concluded that the exposure estimated by this procedure will be within the established ADI (i.e., would represent 37% of ADI for adults, 67% for children and 60% for infants). However, when the MR:TR ratio for 1-day WP was used with the residue data used by the Committee, the calculated GECDE exceeded the ADI by 168% for children and 149% for infants (see Table 5 below). Thus, this approach would not support a 1-day WP and hence data from this time point would not be appropriate for establishing MRLs. The GECDE could not be calculated for 2-day WP as the mean and 95th percentile residue values for this time period was not available in the monograph. However, based on the mean and SD of the residue data presented in Table 7.5 of the monograph, it appears that the estimated GECDE is unlikely to exceed the ADI at 2-day WP. Similarly, GEADE was not calculated as the Committee concluded that no acute reference dose was established.

Table 5. Global estimate of chronic dietary exposure (GECDE) for lasalocid (Source: Table A3.23, A3.24 of the FAO JECFA Monograph 15)

Tissue	Residue (ppb)		MR:TR	Food consumption						Exposure (µg/person)					
	Median	High (p95)		General Population		Children		Infants		General Population		Children		Infants	
				Median	High	Median	High	Median	High	Median	High	Median	High	Median	High
Muscle	25	392	0.25	118	352	35	207	6.3	77	11.80	35.20	3.50	20.70	0.63	7.70
Skin/fat	41.7	561	0.292	1	23	0.05	3	0	0	0.17	3.28	0.01	0.43	0.00	0.00
Offal	123.9	1102	0.088	5	188	0.4	87	0.05	26	0.50	264.70	0.56	122.49	0.07	36.61
Total Exposure (µg/person)*										276.7		126.0		37.2	
Total Exposure (µg/kg bw)**										4.61		8.4		7.4	
% of ADI										92%		168%		149%	

p95 = 95th percentile residue

*Sum of one high exposure and other median exposures

**Body weight for adults of 60 kg, for children of 15 kg and for infants of 5 kg

Theoretical maximum daily intake (TMDI) approach:

Using the MRLs proposed by the JECFA and the MR:TR for 1-day WP, the exposure to consumers estimated based on the TMDI approach is presented in Table 6.

Table 6. Exposure estimates for lasalocid residues based on TMDI approach

Tissue	Proposed MRL (ppb)	Consumption (kg)	MR:TR (1-day WP)	Estimated exposure (µg/person)
Muscle	400	0.30	0.25	480.0
Liver	1200	0.10	0.088	1363.6
Kidney	600	0.05	0.142	211.3
Skin/fat	600	0.05	0.292	102.7
			Total exposure (µg/person)	**2157.6**
			ADI	**300**
			TMDI as % ADI	**719%**

Conclusion:

As both TMDI and GECDE approach do not support the safety of the proposed MRLs, the JECFA could consider establishing MRLs either based on TMDI approach or based on the residue depletion data at 2-day WP (see Table 7). MRLs for lasalocid derived by JECFA using the residue data at 1-day are compared with those that could be proposed if residue depletion data at 2-day WP were used (Table 7). The TMDI approach might yield different MRLs (not presented in this Appendix).

Table 7. MRLs calculated for lasalocid based on residue depletion data at 1-day and 2-day WP (Source: Table 7.5 of the monograph for residue data)

Tissue	No. birds	Mean (ppb)	SD (ppb)	Upper one-sided tolerance (95% CI) of 95th percentile	MRLs (rounded to significant figure)
JECFA proposed MRLs based on 1-day WP					
Muscle	12	65	103	343.7	**400**
Liver	12	244	329	1134.3	**1200**
Kidney	12	128	194	653.0	**600**
Skin/fat	12	106	165	552.5	**600**
MRLs (alternative) derived based on 2-day WP					
Muscle	12	23	23	85.2	100
Liver	12	138	131	492.4	500
Kidney	12	61	70	250.4	250
Skin/fat	12	37	54	183.1	200

Note: The MRLs in bold are those proposed by the 78th JECFA, and those in regular font are those calculated based on 2-day WP residue depletion data.