5. Lasalocid sodium

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Addendum to the monograph prepared by the 78th meeting of the Committee and published in the FAO JECFA Monograph 15.

Background

Lasalocid sodium (hereafter, lasalocid), a divalent polyether ionophore antibiotic, produced by *Streptomyces lasaliensis*, is included as a medicinal additive in feed for continuous use to control coccidiosis in poultry species. It is a broad spectrum anticoccidial agent approved to protect against the *Eimeria* species in broilers and replacement pullets, turkeys, pheasants and quails.

The mechanism of action of lasalocid and other ionophores has been extensively investigated and reported. Like other carboxylic polyether ionophores, lasalocid disturbs ionic homeostasis, leading to osmotic lysis of coccidia.

Lasalocid is not approved for use in laying birds as it partitions into fat (egg yolks) at high concentrations.

Lasalocid was previously reviewed by the Committee at its 78th meeting (FAO, 2013), which established an ADI of 0–5 µg/kg bw, corresponding to an upper bound of acceptable intake of 300 µg/day for a 60 kg person. The ADI is the toxicological ADI, based on the NOAEL of 0.5 mg/kg bw per day from the developmental toxicity study in rabbits and the multigenerational reproductive toxicity study in rats, with application of an uncertainty factor of 100 for interspecies and intraspecies variability. The Committee also recommended MRLs, determined as lasalocid A, in tissues of chickens, turkeys, and quail of 400 µg/kg in muscle, 600 µg/kg in kidney, 1200 µg/kg in liver and 600 µg/kg in skin/fat. Because sufficient data were available to calculate median residue values and the ADI is based on a chronic endpoint, the EDI approach was used to assess exposure. Using the model diet and marker to total residue ratio, based on total residue of toxic concern on "day 0", the ratios are 22% in liver, 41% in kidney, 55% in muscle, and 52% in skin/fat of chicken. The EDI calculated is 80 µg/person *per* day, which represents 27% of the upper bound of the ADI.

At the 22nd Session of the Codex Committee on Residue of Veterinary Drugs in Food (CCRVDF), two conference room documents (CRD) were presented raising concerns for lasalocid. The first CRD form, provided to the CCRVDF session from the European Union, CRD 13 (FAO/WHO, 2015a), was formatted as a Concern Form and considered that the EDI approach does not adequately address disruption of the colonization barrier and proposed that the use of a microbiological ADI end-point and the TMDI approach were the more appropriate

basis for assessing exposure. The concern form also noted that applying the TMDI approach to the recommended MRLs would result in an estimate of human exposure of 882.11 μg/person, which represents 175% of the JECFA microbiological ADI, 504 μg/person. The second conference room document, CRD 27 (FAO/WHO, 2015b), was prepared by Canada and contained comments on Agenda Item 6(c). The comments were subsequently submitted, with minor revisions, in the Concern Form format (FAO, 2015) and considered 1) that the EDI approach may be inappropriate given the variability in the residue depletion data for lasalocid; 2) that the marker to total radiolabelled residue ratio (MR:TRR) from day 0 data was used but the MRLs were based on depletion data from day 1. As the MR:TRR decreases significantly between day 0 and day 1, the use of the MR:TRR for day 0 may underestimate total exposure and it was suggested that using the MR:TRR data from day 1 would be more appropriate; 3) that, if the EDI approach was not applicable, the TMDI approach would result in an estimate of daily human exposure in excess of the ADI; and 4) that using the MR:TRR at day 1 (and, by extension, day 0) would result in exposure exceeding the global estimate of chronic dietary exposure (GECDE) and that the use of day 2 depletion data would be more appropriate. In summary, although the proposed MRLs are based on one of the approaches that JECFA uses, given the potential limitations of the EDI approach when working with highly variable data, Canada expressed concern that the proposed MRLs might expose consumers to residues of lasalocid that are higher than the ADI. CRD 27 also had requested that the JECFA recommend appropriate risk management recommendations to ensure food safety based on unintended exposure of lasalocid to laying hens but this request was not included with the formal Concern Form submission.

The 22nd Session of the CCRVDF requested that JECFA re-evaluate the basis for the ADI and MRLs for lasalocid.

Current evaluation

No new data or studies were provided for the current evaluation. Concerns from two member states, CRD 13 (FAO/WHO, 2015a) and CRD 27 (FAO/WHO, 2015b), plus the resultant Concern Form (FAO, 2015), were evaluated. A comment from the sponsor relating to the toxicological evaluation also was submitted for consideration. Additionally, a numerical error made in the evaluation conducted by the 78th Meeting of JECFA in the entry of day 0 residue depletion data into a spreadsheet (one value was omitted and a second value was reported twice) was discovered and corrected. However, the day 0 residue depletion data are not used to recommend MRLs and this correction does not affect the previous calculations.

Concern from the European Union summarized in CRD 13

This CRD relates to the assignment of the ADI and was not addressed in the residue assessment. The issue has been addressed in a re-assessment of the toxicology of lasalocid by the present meeting of the Committee.

Concern from Canada summarized in CRD 27 and the resultant Concern Form

This CRD (FAO/WHO, 2015b) and the resultant Concern Form (FAO, 2015) relate to the recommended MRLs and have been addressed in the residue evaluation conducted by the present meeting of the Committee:

"Canada would like to raise the following scientific points for further consideration by JECFA:"

Comment 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."

JECFA response: The Committee considered the concern expressed by the Member State. In developing the EDI procedure, the 66th meeting of the Committee (FAO/WHO, 2006) concluded that "the TMDI was no longer the most suitable estimate of chronic intake, because the MRL was a single concentration representing the estimated upper limit of a high percentile of the distribution of marker residue present in a given tissue of the treated animals". The 66th meeting of the Committee concluded that "it was not realistic to use an extreme value of the distribution in a scenario describing chronic intakes. In such a scenario, all concentrations of the distribution of residues should be considered. The median concentration represents the best point estimate of a central tendency over a prolonged period of time, because the concentrations of residues in a given tissue consumed varies from day to day, as reflected in the distribution. Therefore, the Committee decided to use the median of the residue distribution to substitute for the MRL in the intake estimate." While acknowledging that the lasalocid data are variable, the current Committee noted that the EDI approach has been applied in other assessments where residue data were variable. Additionally, the Committee noted that the median is not unduly affected by outliers. Finally, the Committee noted that variability in residue values is not uncommon in studies involving poultry or when dosing via feed. The observed variability associated with lasalocid residue values does not appear to be the result of a systematic bias. The current Committee concluded that the lasalocid residue depletion data are robust, were collected in a GLP-compliant study and can be used with the EDI approach.

Comment 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 perhaps be used along with the residue depletion data in the exposure assessment."

JECFA response: As noted in the monograph prepared for the 78th JECFA (FAO, 2014; see Table 7.2, footnote), the withdrawal times for the radiolabelled residue depletion study are actually 16 hours post last dose relative to their designation (i.e. "0" withdrawal is actually 16 hours post last dose). For the current assessment, all the withdrawal times are restated to clearly indicate the elapsed time from the final dosing. Following this re-presentation of the withdrawal times in the radiolabelled residue depletion study, it is clear that the withdrawal times in that study align more closely to the withdrawal times in the residue depletion study using non-radiolabelled drug than was apparent from Table 7.2 in the monograph prepared by the 78th Meeting of JECFA. The MR:TRR ratios at 16 hours post last dose are 55% (muscle), 52% (skin/fat), 22% (liver) and 41% (kidney).

Using a different approach, interpolated MR:TRR values were developed. For muscle, where there was no MR:TRR at 40 hours post last dose (formerly designated 24 hours withdrawal), the hypothetical 25% MR:TRR for muscle proposed by the requestor was used. The formula ($MR:TRR_{16}$ - $MR:TRR_{40}$)/3 was used to calculate the change-over-time in the MR:TRR ratio between 16 and 40 hours post last dose in 8-hour increments, and this value was then subtracted from $MR:TRR_{16}$ to give $MR:TRR_{24}$. The interpolated MR:TRR ratios at 24 hours post last dose are 45% (muscle), 44% (skin/fat), 18% (liver) and 32% (kidney).

Using either the experimentally derived MR:TRR ratios or those MR:TRR ratios developed through the interpolation, both the EDI and the GECDE remain below the ADI for the general population (Tables 5.1, 5.9), children and infants (Table 5.9). However, because the adjusted sample collection times in the radiolabelled residue depletion study align well with the sampling times in the depletion study using unlabelled drug, the experimentally derived MR:TRR ratios at 16 hours post last dose are used in conjunction with MRLs derived from the 1-day withdrawal residues in the residue depletion study using unlabelled drug in the exposure assessment for lasalocid in chicken tissues.

Comment 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)."

Table 5.1. Comparison of EDIs and GECDEs calculated using various data sets and MR:TRR ratios and the median values indicated.

Calculation parameters			Estimated Exposure
1 day WP medians and 0 day (now designated 16-hour) MR:TRR (from 78th JECFA)	EDI, general population	µg/person/day	80.0
	ADI, general population	%ADI	27
1 day WP medians and 0 day (now designated 16-hour) MR:TRR (from 78th JECFA)	GECDE, general population	µg/person/day	114
	ADI, general population	%ADI	37
1 day WP medians and interpolated 24-hour MR:TRR (from the current assessment)	EDI, general population	µg/person/day	98
	ADI, general population	%ADI	33
1 day WP medians and interpolated 24-hour MR:TRR (from the current assessment)	GECDE, general population	µg/person/day	138
	ADI, general population	%ADI	45

JECFA response: The Committee has concluded that when data are sufficiently robust to support the use of the EDI approach, that approach will be used, because it is more representative of actual exposure from the consumption of tissues derived from treated animals. The lasalocid residue depletion data are robust, were collected in a GLP-compliant study and can therefore be used with the EDI approach (see also the response to #4).

Comment 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)."

JECFA response: Following adjustment of the sampling times in the radiolabelled residue depletion study to clearly reflect the actual time post last dose at which the samples were collected, it is clear that the sampling times in that study and the sampling times in the residue depletion study using non-radiolabelled drug align well and can be used to derive MRLs for the use of lasalocid in chickens. Using the MR:TRR at 16 hours post last dose, both the EDI and the GECDE remain below the upper bound of the ADI for adults, children and infants.

An EDI of 1.33 µg/kg bw (80 µg/60 kg person per day) was calculated, based on median residues for a 1-day withdrawal in chicken, and is equivalent to 27% of the upper bound of the ADI.

The GECDE for the general population is 1.9 µg/kg bw per day, which represents 37% of the upper bound of the ADI. The GECDE for children is 3.4 µg/kg bw per day, which represents 67% of the upper bound of the ADI. The GECDE for infants is 3.0 µg/kg bw per day, which represents 60% of the upper bound of the ADI.

In addition to the numbered questions, the Member State raised the additional concern that they were not able to reproduce the results contained in Table 7.2 of the residue monograph prepared by the 78th meeting of the Committee(FAO, 2014).

JECFA response: The values in Table 7.2 of the JECFA monograph (FAO, 2014) are correctly calculated. For complete transparency, the individual residue values for each animal and each tissue assayed in both the radiolabelled residue depletion study and the residue depletion study using unlabelled drug are presented in the current addendum, Tables 5.2 and 5.4.

Appraisal

No new data or studies were provided for the current evaluation. Two conference room documents (CRDs) were presented at the 22nd Session of the CCRVDF raising concerns for lasalocid. The first CRD form, from the European Union, CRD 13 (FAO/WHO, 2015a), was formatted as a Concern Form. This Concern Form and a comment from the sponsor, relate to the assignment of the ADI, and have been addressed in a re-assessment of the toxicology information available for lasalocid by the present meeting of the Committee. The second conference room document, CRD 27 (FAO/WHO, 2015b), was prepared by Canada; a resultant Concern Form (FAO, 2015) was submitted to the current Committee. The concerns identified by Canada have been addressed in a re-assessment by the present meeting of the Committee of the residue information available for lasalocid and are provided below.

The monograph prepared for the 78th JECFA used data from the day 0 in the radiolabelled study (MacLellan *et al.*, 2003) to calculate the MR:TRR used in the exposure assessment. The mean MR:TRR values presented are correct; however, because mean values were presented in Table 7.2 (FAO, 2014), it is not possible to reproduce the calculated results. In the footnote to Table 7.2, it is stated that 0 hours withdrawal is actually 16 hours after the final dose. All of the MR:TRR ratios in that monograph therefore are for time points 16 hours later than the stated

withdrawal times. Thus, the day 1 MR:TRR data are identified as 24 hours withdrawal but are, in fact, 40 hours after the final dosing. All of the individual data from the radiolabelled residue depletion study (MacLellan *et al.*, 2003) are presented in Table 5.2. All times in Table 5.2 are re-presented to show the correct elapsed time from the last dose.

CRD 27 (FAO/WHO, 2015b) and the related Concern Form (FAO, 2015) from Canada correctly note the significant decrease in MR:TRR between these two sampling points, 16 and 40 hours post-last-dose. However, the MR:TRR ratios are variable and, in fact, increase again at later sampling times. For muscle, there was only one time at which the data were available to calculate the MR:TRR ratio.

Although the 16-hour MR:TRR data remain the most relevant to the exposure assessment, it is possible to use the 16- and 40-hour MR:TRR data to interpolate a hypothetical MR:TRR at 24-hour post dosing. In this alternative approach, interpolated MR:TRR values were determined using the difference between the 16-hour MR:TRR ratio and the 40-hour MR:TRR ratio (including using the 25% value for the muscle MR:TRR proposed in CRD 27 and the related Concern Form at 40 hours (previously identified as 24 hours) for each tissue. The difference was then divided by three to approximate the linear decline over 24hours in 8-hour intervals (*i.e.*, 24 hours/3 = 8 hours). Finally, the 8-hour difference in MR:TRR ratio was subtracted from the 16-hour MR:TRR value to represent an interpolated estimate of the 24-hour MR:TRR value to fully align with the residue depletion data sampling points used to recommend MRLs. Using this linear interpolation, the interpolated MR:TRR values are shown in Table 5.3.

The monograph prepared for the 78th JECFA used the combined residue depletion data from Croubels (2010) and McLellan and King (2006) to calculate the MRLs. This was not clearly identified in the monograph prepared by the 78th Meeting of JECFA (FAO, 2014). While increasing the number of data points available for the MRL determination, this approach lacks transparency and creates a slight disparity between the values used to calculate the recommended MRLs and the values used to calculate the EDI. For the current evaluation, only the depletion data from Croubels (2010) were used (Table 5.4). While using only the Croubels (2010) data set reduced the number of total samples in the assessment, the difference is small. The Croubels (2010) study provides a robust data set of 191 quantifiable residue values from 12 animals from all 4 tissues and 4 withdrawal times; one skin/fat sample at 3 days withdrawal contained residues below the method limit of quantification (LOQ). The McLellan and King (2006) data set contains only 35 residue values above the LOQ, including 24 residue values (6 animals X 4 tissues) at 0 withdrawal. However, at 1-day withdrawal, the McLellan and King (2006) data provide only 11 additional samples (6 liver samples, 3 kidney samples and 2 skin/fat samples). Samples from 2 and 3 days withdrawal are all below the method LOQ. Because the 0-day withdrawal samples are not considered for calculating the MRLs, a total of 72 samples (4 tissues X 12 animals from Croubels (2010) + 4 tissues X 6 animals from McLellan and King (2006)) are not used in the MRL calculation. At 1-day

Table 5.2. Concentrations (µg/kg) of total radiolabelled residues (TRR) and lasalocid residues and resulting MR:TRR (%) (MacLellan *et al.*, 2003).

Time	Tissue	TRR	Lasalocid	MR:TRR	Tissue	TRR	Lasalocid	MR:TRR	Tissue	TRR	Lasalocid	MR:TRR	Tissue	TRR	Lasalocid	MR:TRR
16	Liver	1255	294	0.23	Kidney	403	125	0.31	Skin/Fat	643	342	0.53	Muscle	91	51	0.56
		819	175	0.21		237	119	0.50		145	73	0.50		57	31	0.54
			mean	0.224			mean	0.406			mean	0.518			mean	0.55
40		779	91	0.12		150	27	0.18		166	65	0.39				
		1064	89	0.08		245	28	0.11		122	31	0.25				
		855	41	0.05		158	20	0.13		92	25	0.27				
		609	31	0.05		217	32	0.15		101	22	0.22				
		691	58	0.08						121	34	0.28				
		1030	134	0.13												
			mean	0.086			mean	0.143			mean	0.283				
88		608	94	0.15		115	31	0.27		115	39	0.34				
		840	20	0.02												
		564	60	0.11												

	431	58	0.13						
	392	35	0.09						
	514	31	0.06						
		mean	0.09		mean	0.27		mean	0.34
136	396	23	0.06	49	70	1.43	70	24	0.34
	499	37	0.07	97	28	0.29	81	35	0.43
	402	106	0.26						
		mean	0.13		mean	0.86		mean	0.39

withdrawal, Croubels contributes 48 quantifiable data points (4 tissues X 12 animals) but McLellan and King (2006) contributes only 11 quantifiable data points, as noted above. Considering all available data points from 1-day withdrawal onward, using the data from Croubels (2010) provides 143 quantifiable data points (*vs.* 154 when the data are combined with the 11 quantifiable data points from McLellan and King (2006)). Tissue medians, means, and upper tolerance limits based on the data from Croubels (2010) are presented in Table 5.5.

Table 5.3. Interpolated MR:TRR values (%) between 16- and 40-hours post last dose sampling (MacLellan *et al.*, 2003).

Tissue	Time	MR:TRR	8 h interval change in MR:TRR
Liver	16	22.4	4.6
	24	17.8	
	32	13.2	
	40	8.6	
Kidney	16	40.6	8.8
	24	31.8	
	32	23.0	
	40	14.3	
Skin/Fat	16	51.8	7.8
	24	44.0	
	32	36.1	
	40	28.3	
Muscle	16	55.0	10
	24	45.1	
	32	35.1	
	40	25.0	

* $(MR:TRR_{16}-MR:TRR_{40})/3$; this value is then subtracted from $MR:TRR_{16}$ to give $MR:TRR_{24}$.

Table 5.4. Residue depletion data (µg/kg)(Croubels, 2010).

Withdrawal Time (d)	Kidney	Muscle	Liver	Skin/Fat
0	810.27	337.47	1628.35	947.6
0	1667.45	627.25	2801.57	1462.62
0	1180.53	402.28	1917.63	1056.72
0	1354.99	538.1	2015.38	1211.63
0	1432.27	533.76	2092.25	1491.66
0	851.54	345.1	1360.06	1129.46
0	663.5	281.58	1640.54	576.51
0	883.08	414.77	1810.6	977.57
0	737.24	372.83	1564.45	677.15
0	1414.19	774.2	2051.58	1216.14
0	792.7	335.48	1769.49	828.49
0	815.96	400.21	1430.63	905.03
1	17.93	13.5	50.17	42.72
1	54.04	32.4	168.48	28.78
1	73.41	25.25	145.15	49.62
1	44.86	24.77	102.6	30.49
1	68.4	32.65	165.24	40.86
1	45.96	16.09	79.85	29.48
1	427.68	294.35	832.17	334.31
1	23.11	8.26	40.36	16.88
1	33.7	14.83	60.13	42.57
1	44.35	14.58	82.84	31.25
1	73.77	26.21	156.74	69.7
1	633.11	276.79	1038.88	554.3

2	90.78	54.62	351.47	89.07
2	27.64	10.89	73	12.24
2	28.96	14.83	76.81	14.17
2	43.4	20.57	92.49	16.11
2	79.7	15.38	218.46	34.73
2	274.12	83.8	444.18	191.88
2	28.86	10.35	47.32	14.82
2	44.7	16.74	91.87	19.6
2	22.26	10.94	79.28	10.96
2	24.16	8.86	38.63	9.03
2	35.9	13.91	85.04	14.85
2	34.97	14.64	57.71	11.43
3	19.95	8.14	47.46	8.4
3	23.29	8.77	45.46	9.29
3	33.36	12.07	160.98	20.2
3	43.82	14.06	120.72	14.98
3	17.1	9.25	41.54	6.78
3	16.05	5.12	29.12	10.09
3	30.99	8.17	71.21	9.72
3	45.29	10.53	194.4	8.97
3	32.11	6.39	68.53	9.11
3	15.78	6.26	27.8	7.44
3	15.69	5.9	22.71	<LOQ
3	23.77	6.52	36.75	10.27

LOQ = 5 µg/kg.

Table 5.5. Upper tolerance limits (µg/kg) based on Croubels (2010).

	Time (day)	Kidney	Muscle	Liver	Skin/Fat
Median	0	867.31	401.25	1790.05	1017.15
Mean		1050.31	446.92	1840.21	1040.05
SD		338.84	144.06	385.42	281.75
N		12.00	12.00	12.00	12.00
K		2.71	2.71	2.71	2.71
UTL		1967.21	836.74	2883.15	1802.46
Median	1	50.00	25.01	123.88	41.72
Mean		128.36	64.97	243.55	105.91
SD		193.66	103.39	329.30	165.40
N		12.00	12.00	12.00	12.00
K		2.71	2.71	2.71	2.71
UTL		652.39	344.75	1134.62	553.47
Median	2	35.44	14.74	82.16	14.84
Mean		61.29	22.96	138.02	36.57
SD		70.43	22.71	130.99	53.66
N		12.00	12.00	12.00	12.00
K		2.71	2.71	2.71	2.71
UTL		251.88	84.40	492.49	181.77
Median	3	23.53	8.16	46.46	9.29
Mean		26.43	8.43	72.22	10.48
SD		10.62	2.70	56.39	3.85
N		12.00	12.00	12.00	11.00
K		2.71	2.71	2.71	2.78
UTL		55.18	15.74	224.82	21.19

UTL = Upper one-sided 95% Tolerance Limit.

Using the MR:TRR from MacLellan *et al.*, 2003, at withdrawal time 16 hours (previously designated 0 hours), and the median values for the tissues from Croubels (2010), at day 1 (24 hours) withdrawal, the EDI provided in the residue monograph prepared by the 78th meeting of the Committee (FAO, 2014; see Table 7.10) is as shown in Table 5.6.

Table 5.6. EDI (µg/kg) provided in the 78th JECFA (Table 7.10) (FAO, 2014).

Tissue	Median	MR:TRR	Consumption	Exposure
Liver	123.9	0.22	0.100	56.3
Kidney	50.0	0.41	0.050	6.1
Muscle	25.0	0.55	0.300	13.6
Skin/Fat	41.7	0.52	0.050	4.0
Total				80.0
% ADI				26.7

Using the interpolated MR:TRR at 24 hours post-last-dose from Table 5.3 above, and the median values for the tissues from Croubels (2010) alone at day 1 withdrawal, the EDI is shown in Table 5.7.

Table 5.7. EDI (µg/kg) using interpolated MR:TRR at 24 hours post-last-dose from Table 5.3 above and the median values for the tissues from Croubels (2010) alone at day 1 withdrawal.

Tissue	Median	MR:TRR	Consumption	Exposure
Liver	123.9	0.18	0.100	68.8
Kidney	50.0	0.32	0.050	7.8
Muscle	25.0	0.45	0.300	16.7
Skin/Fat	41.7	0.44	0.050	4.7
Total				98.0
% ADI				33

A comparison of the EDIs for the general population, using various data sets, is shown in Table 5.8.

Table 5.8. Comparison of EDIs calculated using various data sets and MR:TRR ratios and the median values indicated.

Calculation parameters			Estimated Exposure
1 day WP medians and 0 day (now designated 16-hour) MR:TRR (from 78th JECFA)	EDI, general population	µg/person/day	80.0
	ADI, general population	%ADI	27
1 day WP medians and extrapolated 24-hour MR:TRR (from the current assessment)	EDI, general population	µg/person/day	98
	ADI, general population	%ADI	33
0 day WP medians and 0 day (now designated16-hour) MR:TRR (from CRD 27 and Concern Form)*	EDI, general population	µg/person/day	1373.4
	ADI, general population	%ADI	458
1 day WP medians and MR:TRR (from CRD 27 and Concern Form)	EDI, general population	µg/person/day	195.5
	ADI, general population	%ADI	65

* The 0-day withdrawal data were not considered appropriate for establishing MRLs or determining exposure. They are included here because they were presented in CRD27 and in the Concern Form.

In recommending MRLs for lasalocid in poultry food commodities, the 78th Meeting of the Committee considered the following factors:

- An ADI of 0-5 µg/kg of body weight was established by the Committee. The upper bound of the ADI is equivalent to 300 µg lasalocid sodium for a 60 kg person.
- Where information on approved veterinary uses was provided, withdrawal times were in the range 0-7 days.
- Lasalocid sodium is extensively metabolized in poultry, although the metabolites were not identified.
- Lasalocid A is a suitable marker residue in all edible tissues of poultry.
- Lasalocid A represents conservatively 22% of lasalocid sodium in liver, 41% in kidney, 55% in muscle, and 52% in skin/fat in chicken;
- Extension of MRLs to turkey and quail and the extrapolation of MRLs to pheasant are appropriate as depletion data were available, the marker residue was demonstrated and information was available on authorized uses.

- Validated LC-MS/MS and HPLC methods were provided and considered suitable for routine monitoring of lasalocid A as marker residue in poultry tissues.

The MRLs recommended for chicken, turkey, quail and pheasant tissues were based on the upper limit of the one-sided 95% confidence interval over the 95th percentile (UTL 95/95) for the 1-day post-treatment data from the unlabelled residue depletion study in chicken.

The MRLs recommended for chicken, turkey, quail and pheasant by the 78th Meeting of the Committee were 1200 µg/kg in liver, 600 µg/kg in kidney, 400 µg/kg in muscle and 600 µg/kg in skin plus fat.

An EDI of 1.33 µg/kg body weight per day (80 µg/60 kg person per day) was calculated, based on median residues for a 1-day withdrawal in chicken, equivalent to 27% of the upper bound of the ADI. The GECDE for the general population based on median residues for a 1-day withdrawal was 1.9 µg/kg body weight per day, which represents 37% of the upper bound of the ADI; the GECDE for children and infants was 3.4 µg/kg body weight per day and 3.0 µg/kg bw per day resp., which represents 67% and 60% of the upper bound of the ADI.

The current Committee reviewed these MRL recommendations, based on the dietary exposure evaluation in the following section and the decision by the present Committee to retain the ADI of 0-5 µg/kg of body weight established by the 78th Meeting of the Committee. The question of residue carry over into eggs was deferred pending the outcome of an electronic working group established by the 22nd Session of the CCRVDF.

Dietary Exposure Assessment

An EDI of 80 µg/person per day was calculated, based on median residues for a 1-day withdrawal in chicken, and are equivalent to 27% of the upper bound of the ADI (see Table 5.7).

In addition, the Committee calculated GECDE values to be compared with the EDI. In this additional dietary exposure assessment, poultry muscle, fat and skin and offal were contributors to dietary exposure. Calculated GECDE values for lasalocid for the general population, children and infants are shown in Table 5.9.

Using the median residue as inputs, the GECDE for the general population was 1.85 µg/kg bw/day, which is equivalent to 37% of the upper bound of the ADI. In children the GECDE was 3.38 µg/kg bw/day which represents 68% of the upper bound of the ADI. Exposure of infants was estimated to be lower at 2.99 µg/kg bw/day, 60% of the upper bound of the ADI.

Maximum Residue Limits

Following consideration of the issues raised in the concern forms, the ADI established and MRLs recommended at the seventy-eighth meeting of JECFA remain unchanged.

Table 5.9. Calculated GECDE values for lasalocid for the general population, children and infants.

Category	Type	Median concentration[1] (µg/kg)	Mean consumption[2] whole population, g/d	97.5th consumption[3] consumers only, g/d	MR:TR ratio[1]	Exposure (µg/kg bw/day)		GECDE[4]	
						Mean	97.5th	µg/kg bw/day	%ADI
				General Population					
Poultry	Poultry muscle	25.0	118.0	352	0.55	0.09	0.27	0.09	1.8
Poultry	Poultry fat and skin	41.7	1.0	23	0.52	0.00	0.03	0.00	0.0
Poultry	Poultry offal	123.9	5.0	188	0.22	0.05	1.76	1.76	35.2
TOTAL						0.1	1.8	1.85	37
				Children					
Poultry	Poultry muscle	25.0	35.0	207	0.55	0.11	0.63	0.11	2.2

Poultry	Poultry fat and skin	41.7	0.1	3	0.52	0.00	0.02	0.00	0.0
Poultry	Poultry offal	123.9	0.4	87	0.22	0.02	3.27	3.27	65.4
TOTAL						0.1	3.3	3.38	68
				Infants					
Poultry	Poultry muscle	25.0	6.3	77	0.55	0.06	0.70	0.06	1.1
Poultry	Poultry fat and skin	41.7	-	-	0.52	-	-	-	-
Poultry	Poultry offal	123.9	0.1	26	0.22	0.01	2.93	2.93	58.6
TOTAL						0.1	2.9	2.99	60

[1]Median concentration at 1 day; [2]highest mean consumption figures based on whole population considered from the available dataset; [3]highest 97.5th food consumption figures based on consumers only considered from the available dataset; [4]GECDE is the sum of the highest exposure at the 97.5th percentile of consumption for a food and the mean dietary exposures of the other foods.

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