LINCOMYCIN

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ADDENDUM

To the monograph prepared by the 54th meeting of the Committee and published in the FAO Food and Nutrition Paper 41/13

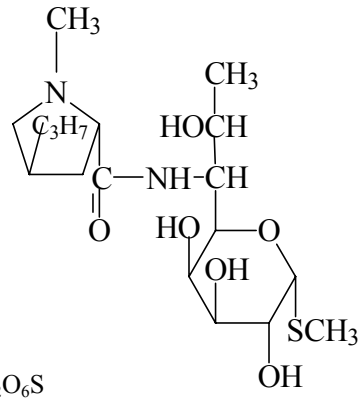
IDENTITY

Chemical name: Methyl 6,8-dideoxy-6-[[(1-methyl- 4-propyl-2-pyrolidinyl)carbonyl]amino]-1-thio-D-urethra-α-D-galacto-octopyranoside (CAS name)

Methyl 6,8-dideoxy-6-(1-methyl *trans*-4-propyl-L-2-pyrolidone-carboxamido)1-thio-D-erythro-α-D-galacto-octopyranoside (IUPAC name)

CAS Number: 154-21-2 (free base)

Structural formula:



Molecular formula: $C_{18}H_{34}N_2O_6S$

Molecular weight: 406.56

INTRODUCTION

Lincomycin alone or in combination with other drugs is given orally to poultry and pigs for the treatment of bacterial enteric infections, control of respiratory infections and for growth promotion. The maximum recommended therapeutic dose in chickens is 50 mg/kg body weight/day and for pigs, 13 mg/kg body weight/day. Combination preparations with neomycin are used as intra-mammary applications in lactating dairy cattle for treatment of acute mastitis.

Lincomycin has previously been evaluated by the Committee at its 54th meeting. The Committee established an ADI of 0-30 μg of lincomycin per kg of body weight per day. It recommended the following MRLs (table 1):

Table 1. Maximum Residue Limits (MRLs) of lincomycin recommended by the 54th meeting of the FAO/WHO Joint Expert Committee on Food Additives

Species/Tissue	MRLs [µg/kg]				
	Liver	Kidney	Muscle	Fat	Milk
Cattle	500[a]	1500[a]	100[a]	100[a]	150
Pigs	500	1500	100	100	
Sheep	500[a]	1500[a]	100[a]	100[a]	
Chickens[c]	500[a]	1500[a]	100[a]	100[a,b]	

[a] Temporary MRL [b]skin/fat [c] the Committee was unable to recommend an MRL for lincomycin in eggs

At this meeting the Committee requested the following information:

1. Data from residue depletion studies in cattle, sheep and chickens which show that lincomycin is the major microbiologically active residue in the edible tissues.
2. Data from residue depletion studies showing that lincomycin is the major microbiologically active residue in chickens' eggs.
3. The results of a residue depletion study in which GC-MS is used to analyse residues in chickens' eggs.

RESIDUES IN FOOD AND THEIR EVALUATION

New studies

The sponsor provided five new study reports for consideration by the Committee - three studies conducted with broiler chickens and two studies on pigs. The sponsor indicated that because of the age of the compound, the generic nature of the substance and its market size, further work on other species was not warranted and no data were provided. The new data in chickens address that parent lincomycin is the major residue component with significant microbiological activity. The new studies in pigs indicate that for muscle and fat, the MRLs recommended for these tissues may not be adequate considering the accepted good practice in the use of veterinary drugs.

Review of the temporary MRLs for chickens

Three types of residue depletion studies - all conducted using medicated drinking water for the administration of the drug - were reviewed by the Committee:

1. A study using ^{14}C-labelled lincomycin which had already been reviewed by the 54th meeting of the Committee.
2. A new study in which the depletion of lincomycin was determined by gas chromatography and mass spectrometry (GC-MS).
3. Two similarly designed new studies in which the depletion of antimicrobial activity was determined using a microbiological inhibition test (*Micrococcus luteus* ATTC 9341).

Using the results of these studies, the following calculations were performed in order to test the proposed dose linearity:

1. All dose rates of lincomycin or its salts used in the studies were re-calculated, where necessary, to uniformly represent free active lincomycin base (unit: mg/kg of body weight/day).
2. Parameters describing the depletion of residues were estimated for each study using linear regression analysis of the data on the basis of equation [I].

$$\log_{10} C_t = \log_{10} a + b \times t \qquad [\text{I}]$$

   where C_t is the predicted concentration of the residue at t, a given withdrawal time, a is the concentration extrapolated for zero withdrawal time and b is a rate constant describing the depletion. For all studies and all calculations t was expressed in hours.
3. A relationship between the extrapolated concentrations of residues for zero withdrawal time (antilog of parameter a) and the applied doses was established and tested for linearity.

Residue depletion study with ^{14}C-labelled lincomycin

An equal number of 25 days old male and female Hubbard-cross-Hubbard chicks were given water containing ^{14}C-lincomycin hydrochloride, equivalent to 34 µg of lincomycin free base/mL (specific activity 2.47 µCi/mg) from day-of-age 35 through 41 (7 days). This dose concentration corresponds to approximately twice the typical recommended concentration of 64 mg/gallon. The body weights of the animals were determined on days 1 and 7 of treatment. Water intake was measured daily. Generally, the males had higher initial body weights, gained body weight more rapidly and drank more water. The average dose rate (calculated on the basis of free lincomycin base) was approximately 5.31

mg/kg of body weight/day (5.47 mg/kg of body weight per day for the males and 5.15 mg/kg of body weight per day for the females). From day-of-age 42 through termination, drug-free water and feed were provided. Six birds (3 males and 3 females) served as controls. Three males and three females were sacrificed at 0, 12, 24, 48, 96, and 168 hours withdrawal of the medicated water. Samples of blood, skin/fat, muscle (red : white muscle in 1:1 proportion), liver, and kidney were removed from the carcass.

Total radioactivity was determined by combustion analysis of aliquot amounts of the tissues. The residues of lincomycin were further characterized following tissue extraction, solvent partition and chromatographic fractionations. Up to 96 hours withdrawal time most of the total residue was extractable (Hornish et al., 1984).

The results of the statistical calculations are summarized in table 2.

Table 2. Parameters of linear regression analysis of the data describing the depletion of ^{14}C-labelled residues in tissues of chickens treated orally with ^{14}C-lincomycin

Tissue	Type of residue	Sex of the animals	Parameters of the linear regression			Antilog (*a*)
			a	b	r	
Muscle	"total residue"	male	1.507	-0.0049	-0.6218	32.1
		female	1.635	-0.0078	-0.9118	43.2
		both sexes	1.577	-0.0064	-0.7804	37.8
Skin/fat	"total residue"	male	2.017	-0.0083	-0.7349	104
		female	1.877	-0.0085	-0.7300	75.3
		both sexes	1.937	-0.0083	-0.7159	86.5
Liver	"total residue"	male	2.761	-0.0143	-0.8601	577
		female	2.996	-0.0180	-0.9417	999
		both sexes	2.892	-0.0163	-0.9020	780
Liver	^{14}C-lincomycin	both sexes	1.986	-0.0229	-0.9493	96.8
Kidney	"total residue"	male	2.745	-0.0137	-0.9013	556
		female	2.917	-0.0173	-0.9103	826
		both sexes	2.840	-0.0156	-0.9011	692

Depletion of parent lincomycin as determined by gas chromatography/mass spectrometry (GC-MS)

In a new study (Hornish and Glavanowich, 2000), equal numbers of male and female 1-2 day-old chicks were given a combination of lincomycin and spectinomycin dissolved in drinking water. Raw data on dose rates and body weights of the animals were not provided. However, according to the report, concentrations of free active lincomycin in the drinking water were 286.6 mg/L for the first period of seven consecutive days (resulting in a mean dose rate of 172.4 mg of lincomycin/kg of body weight). This was followed by a 7-day period of exposure to non-medicated water and a second exposure to drinking water containing 57.1 mg of lincomycin/L) for a period of seven consecutive days (resulting in a mean dose rate of 20.4 mg of lincomycin/kg of body weight). Twelve birds were sacrificed at each of four time points after the second exposure period (0, 2, 7, and 14 days following withdrawal of the medicated drinking water). Samples were collected as 4-bird composites. However, only the 0-day, 2-day and 7-day slaughter groups were assayed for lincomycin. The tissues were analysed using a GC-MS procedure for the quantitative determination of parent lincomycin. The parameters of the linear regression analysis of the results of these analyses are given in Table 3.

Table 3. Parameters of linear regression analysis of the depletion of parent lincomycin from tissues of chickens treated orally with a combination of lincomycin/spectinomycin

Tissue	Parameters			Antilog (*a*)
	a	b	r	
Muscle	[1.593]$^{+)}$			39.2
Skin/fat	1.958	-0.0057	-0.9651	90.8
Liver	2.917	-0.0330	-0.9773	826
Kidney	2.920	-0.0337	-0.9875	831

$^{+)}$ In the absence of suitable kinetic data the geometric mean of three data points at zero withdrawal time was calculated

Depletion of antimicrobial activity as determined by microbiological inhibition tests

Two new studies were reported in which the microbiologically active residues were determined after treatment of chickens with lincomycin in drinking water (Ibayashi and Schiemer, 1992a; Ibayashi and Schiemer, 1992b). The studies

were identical in design except that female birds were used in one study and animals of both sexes were used in the second study.

Female broiler chickens were treated with LINCOMIX® for 7 consecutive days. The dosages used were 16mg/L and 48 mg/L, respectively (Ibayashi and Schriemer, 1992a). From the details given in the report on body weights and drug intake, an average dose rate of approximately 7.1 mg of free active lincomycin/kg of body weight was calculated for the higher dose group. Birds were slaughtered at 2, 6, 12, 24, 48, 72, 96, and 120 hours post antibiotic treatment. Six treated birds were slaughtered per time point. Residues were determined from pooled tissues of two birds using a microbiological inhibition test (*Micrococcus luteus* ATTC 9341). Only the results obtained with the high dose group could be used for statistical calculations. Because of the low concentration of residues in muscle and fat/skin, results were only tabulated for time points up to 24 hours in these tissues. In the tissues of the low-dose group too many concentrations of the residues of lincomycin were below the limit of detection of the method to enable statistical calculations.

The study was repeated using the same design with mixed-sex broiler chickens. The average dose rate was approximately 6.6 mg of free active lincomycin/kg of body weight per day in the high-dose group and 2.34 mg/kg of body weight per day in the low-dose group (Ibayashi and Schriemer, 1992b). Table 4 shows the results of the linear regression analysis of the data obtained in the two studies.

Table 4. Parameters of linear regression analysis of the depletion of antimicrobial residues from liver and kidney of chickens treated orally with lincomycin

Tissue	Sex of the birds	Dose [mg/kg of body weight]	Parameters			Antilog (*a*)
			a	b	r	
Liver	female	7.1	2.2524	-0.0331	-0.8765	179
	mixed sex	2.34	2.0964	-0.0928	-0.8161	125
		6.6	2.3648	-0.0631	-0.8080	232
Kidney	female	7.1	2.4269	-0.0351	-0.7160	267
	mixed sex	2.34	1.9862	-0.0545	-0.7353	96.9
		6.6	2.4239	-0.0389	-0.7833	265

Testing of the hypothesis of dose-linearity

Estimates of the concentrations of residues of lincomycin at zero withdrawal time of the medicated drinking water ("on-treatment"-concentrations) were obtained by calculating the antilog of the parameters *a* given in tables 2, 3, and 4. A relationship between the doses administered to the animals in the various studies and these statistically estimated concentration was established. As shown in equations II a and II b and in figure 1, there is an acceptable linear relationship (r = 0.9774 for the liver data and 0.9994 for the kidney data) over the whole range of dose rates. The relationship found is:

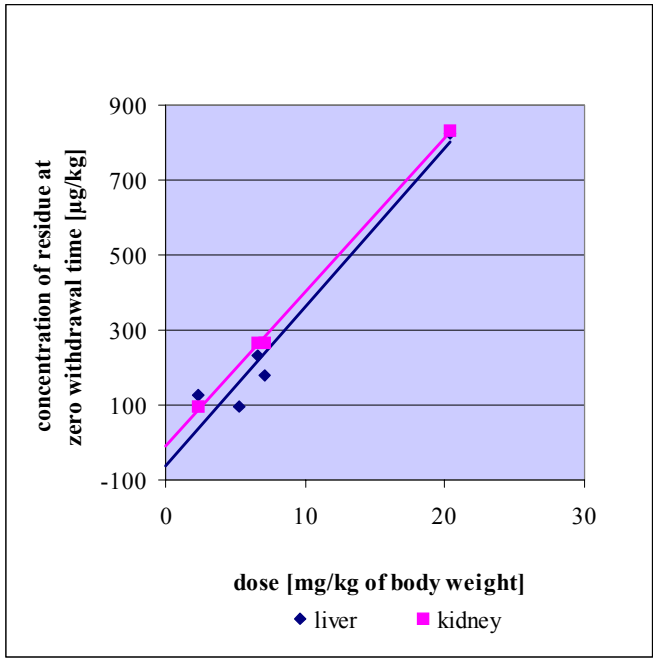
$$C_{lincomycin}[\mu g / Kg]_{liver} = -62.42[\mu g / Kg] + 0.04239 \times dose_{lincomycin}[mg / Kg] \quad \text{[IIa]}$$

$$C_{lincomycin}[\mu g / Kg]_{kidney} = -8.13[\mu g / Kg] + 0.04098 \times dose_{lincomycin}[mg / Kg] \quad \text{[IIb]}$$

For kidney the relationship found is almost the same as the one found for liver (see also figure 1). For skin/fat and muscle such relationship could not be established due to lack of suitable data. The concentrations of lincomycin in these two tissues were generally low and the kinetics of depletion could usually not be followed by the available analytical methods.

Since lincomycin had been determined in the above mentioned studies using three different analytical detection principles (radioactivity, mass spectra, inhibition of microbial growth), it can be concluded from the observed dose-linearity that parent lincomycin is the major microbiologically active residue in liver and kidney.

Figure 1. Relationship between the daily doses of orally administered lincomycin and the extrapolated concentration of residues of lincomycin at zero withdrawal time



Data base for re-consideration of MRLs for chickens

Table 5 (next page) summarizes the information on which the setting of MRLs could be based. In order to obtain initial crude estimates, two approaches were used. In the first approach "statistical tolerance limits" (= upper limits of the 95% confidence interval for the upper one-sided tolerance limits on the 95th percentile) were calculated using the parameter estimates obtained in the linear regression analysis. This would always be the preferred way if a sufficient number of data points would be available. Unfortunately, this was typically not the case in the majority of the available studies. Therefore, a critical review of table 5 shows that this approach was not always justified and the results obtained were variable. This variability could be reduced by following the second approach in which the geometric mean plus three standard deviations was used. However, the major weakness of this way of calculation is that with small numbers of data points resulting estimates of MRLs are likely to be too low to accommodate variable results. Although the data base on which MRLs for chicken tissues could be based was still rather limited, the following conclusions could be made: The MRLs for liver and kidney in chickens should be numerically identical. The MRL for skin/fat should be about three times as high as the MRL for muscle tissues in chickens.

Review of the MRLs for pigs

The following studies were reviewed by the Committee:

Four groups of pigs (body weight range 49-75 kg) were treated with lincomycin hydrochloride hemihydrate at 0, 47.6 ±4.97, 114.9 ±26.14, or 210.5 ±69.44 g of lincomycin free base equivalents/1000 kg of feed for seven consecutive days. Inhomogeneities were reported in the high dose feed. Mean feed consumption levels were 2.911, 2.445, 2.680 and 2.470 kg of feed/animal/ day in the control group and in the three treatment groups, respectively. Treated animals were euthanized at 3, 6, 12, 24, or 48 hours following last treatment. Tissues of individual animals were not collected until all animals from each time point had been euthanized. The liver and kidney were assayed by GC-MS after nine months of storage at -20 °C. The liver and kidney samples were analyzed in two different laboratories (Nappier et al., 1996a, Nappier et al., 1996b, Nappier et al., 1997).

The results of the analyses of edible tissues obtained from the animals receiving the highest dose are shown in figure 2 (p 51). The parameters of the linear regression analysis of the data are given in table 6 (p 51). There was a good linear correlation between the concentration of the drug in the administered feed and the resulting concentrations of residues in the edible tissues.

Table 5. Data base for re-consideration of MRLs for chickens

Dose [mg/kg bw /day]	Withdrawal time [hours]	Basis: "Statistical tolerance limits" at zero withdrawal time[1a)]						Basis: "Mean plus three standard deviations"[1b)]					
		Liver	Kidney	Muscle	Skin/Fat	Intake [µg/day]	Comment	Liver	Kidney	Muscle	Skin/Fat	Intake [µg/day]	Comment
		[µg/kg] (number of data available)						[µg/kg] (number of data available)					
20.4	0	6776 (6)	4058 (6)		230 (9)		2),3)	1205 (3)	1204 (3)	47 (3)	277 (3)	209	2)
		2311 (28)	[1924] (28)	64 (28)	281 (28)	360	4), 5)	2190 (5)	[2925] (5)	74 (5)	270 (5)	401	2),4),5)
7.1	0	561 (12)	2305 (12)										
	2							445 (3)	416 (3)	143 (3)			2),6)
6.6	0	1310 (9)	849 (9)				2),7)						
	2							364 (3)	442 (3)				2),7)
5.3	0	3517 (28)	2951 (28)	102 (28)	412 (28)	551	8)	3421 (5)	4339 (5)	114 (5)	408 (5)	614	2), 8)
		437	[367]	16	74	71		574 (5)	[728] (5)	21 (5)	65 (5)	103	2)
2.34	0	1189 (5)	966 (6)				2),7)						2)
	2							311 (3)	617 (3)				2),6),7)

1a) "Statistical tolerance limits" means the upper limit of the 95% confidence interval for the upper one-sided tolerance limits on the 95th percentile.
1b) "Mean plus three standard deviations" refers to the geometric mean.
2) The number of data points available for this type of calculation is very low.
3) The original data were used as given in the report of the study.
4) The results of the "total residue study" (Hornish et al., 1984) were transformed to express residues of parent lincomycin. These data were multiplied with 20.4/5.3 to extrapolate to the highest dose rate used. All calculations were subsequently performed using this base of extrapolated data.
5) Data in [ ]: The same factor was used for liver and kidney to calculate parent drug from total residue.
6) Data at zero withdrawal time were not available.
7) At dose rate 6.6 the variability of the data is much lower than at dose rate 2.34. The high values of both, the tolerance limits and of mean + 3sd at the lower dose are mainly caused by the high variability of the data and the low number of data points.
8) The figures represent "total residue".

Figure 2. **Results of a tissue residue depletion study with pigs treated orally with approximately 210 mg lincomycin per kg of feed**

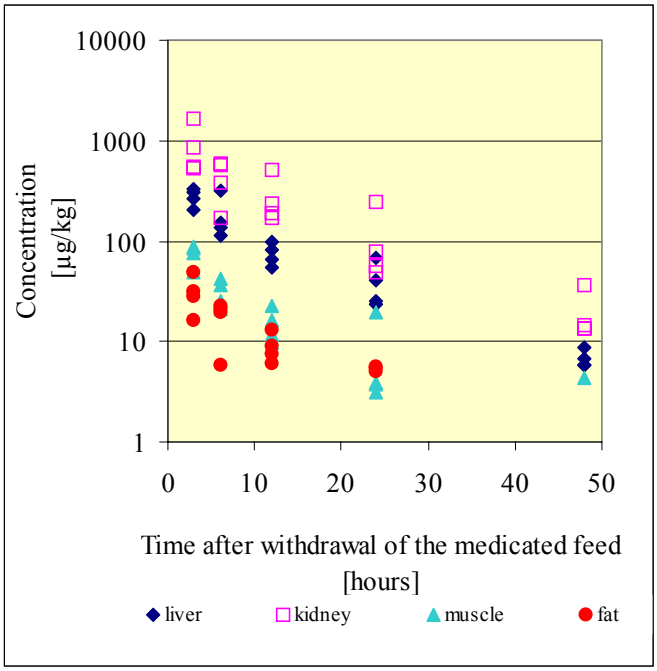
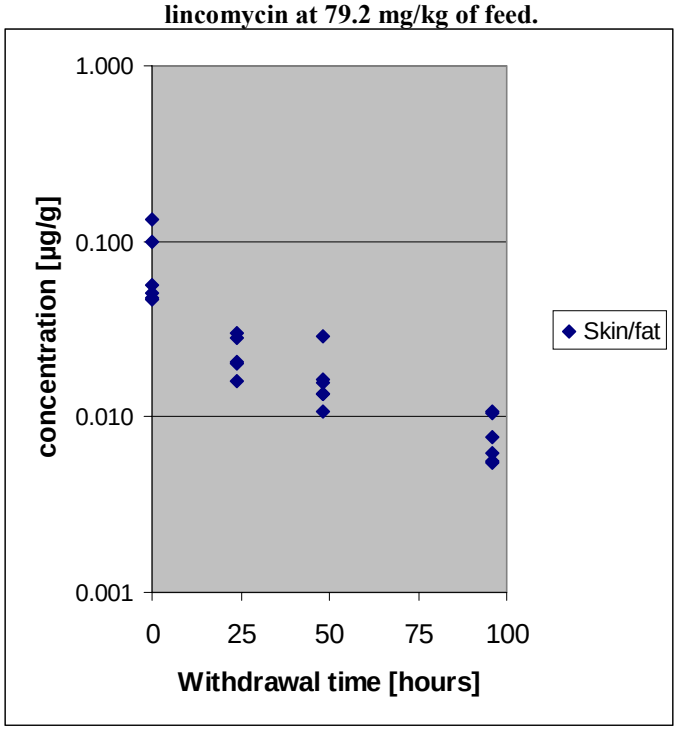


Table 6. **Parameters of the linear regression analysis of the depletion of parent lincomycin tissues of pigs treated orally with lincomycin at 210.5 mg/kg of feed**

Tissue	Parameters				Antilog a
	a	b	r	n	
Liver	2.412	-0.0341	-0.9634	20	258
Kidney	2.861	-0.0348	-0.9246	20	726
Muscle	1.670	-0.0321	-0.7800	17	46.8
Fat	1.341	-0.0178	-0.7039	15	21.9

In a recently completed study lincomycin was administered to pigs in feed using a Linco-Spectin® premix. The concentration of lincomycin was approximately 80mg/kg of feed. Five groups of six pigs each were provided the premix *ad libitum* for 30 days. The resulting dose rate was 3.25-3.67 mg lincomycin/kg of body weight per day (Nappier et al., 2001). Groups of animals were sacrificed immediately after withdrawal of the medicated feed and at 1, 2, 4 and 7 days. The results of this study fitted generally well into the linear correlation seen in the previous study reports between drug concentrations in feed and residue concentrations in edible tissues. However, when using linear extrapolation from the 79.2 mg/kg concentration in feed to the highest concentration of approximately 210 mg/kg, the concentrations of lincomycin in skin with adhering fat were unexpectedly high and the concentrations in muscle were slightly higher than expected. The results of the analyses of skin with adhering fat are shown in figure 3. Using linear regression, the kinetics of depletion could be described by the following parameters: a = 1.7062, b = -0.0094, r = -0.8961 (n = 23).

Figure 3. **Depletion of lincomycin residues in skin/fat of pigs treated orally with lincomycin at 79.2 mg/kg of feed.**



In contrast to the situation in chickens, a larger number of data points was available in the relevant study. Therefore, it was possible to calculate more meaningful estimates of "statistical tolerance limits" as a starting point for re-consideration of the MRLs. Table 7 provides such estimates for different combinations of the upper limit of the 1- α confidence interval for the one-sided upper tolerance limit of the fraction 1- γ of the population, and for different withdrawal times.

The pig studies available to the Committee at this meeting indicate that the concentrations of residues of lincomycin were significant in skin/fat and were somewhat higher in muscle than expected from the earlier residue studies reviewed by the 54th Committee. In contrast to chickens, concentrations of residues in kidney and liver differed by a factor of approximately three.

Table 7. "Statistical tolerance limits" and "Theoretical Maximum Daily Intakes" as a function of drug withdrawal time in pigs treated orally with approximately 210 mg lincomycin/kg of feed[*)]

Withdrawal time [hours]	Statistical certainty		Confidence interval limits in tissues					Estimates of intake	
			Liver	Kidney	Muscle	Fat	Skin/Fat	TMDI [µg/person/day]	
	1-γ	1-α	Concentration of lincomycin residues [µg/kg]					Liver Kidney Muscle Fat	Liver Kidney Muscle Skin/Fat
0	0.95	0.95	670	3076	310	98	365	319	332
	0.99	0.95	934	5077	580	165	515	529	547
	0.99	0.99	1208	7497	1018	277	656	815	834
6	0.95	0.95	408	1827	185	73	316	191	204
	0.99	0.95	571	3036	351	123	448	320	336
	0.99	0.99	731	4418	601	191	567	484	503
12	0.95	0.95	250	1099	115	55	275	117	183
	0.99	0.95	351	1837	219	94	390	197	303
	0.99	0.99	447	2648	371	154	491	296	451
18	0.95	0.95	155	673	75	44	239	74	126
	0.99	0.95	218	1126	142	74	339	124	210
	0.99	0.99	277	1618	241	122	427	187	310
24	0.95	0.95	97	419	51	36	208	48	82
	0.99	0.95	137	700	95	60	296	80	136
	0.99	0.99	174	1009	165	100	371	122	200

[*)] The data for skin/fat were extrapolated from a study in which the concentration in the feed was 79.2 mg/Kg

MAXIMUM RESIDUE LIMITS

The sponsor has provided responses to the request for additional data for pigs and chickens. However, because of the age of the compound, its generic nature, and the availability of other antimicrobial agents for the intended uses, has indicated that they will no longer support lincomycin for use in cattle and sheep.

In reviewing the maximum residue limits recommended at its 54th meeting the Committee took into account the following factors:

- The ADI of 0-0.30 µg /kg of body weight allocated by the Committee at its 54th meeting was based on a microbiological end-point. This ADI is equivalent to an acceptable maximum daily intake of 1800 µg of antimicrobially active residues of lincomycin for a 60-kg person.
- Parent lincomycin is the only residue with significant antimicrobial activity in tissues of chickens and pigs.
- Kidney and liver contain the highest concentrations of residues in chickens and pigs, however, the new studies confirm that the concentrations of residues in kidney and liver are similar in chickens but differ by a factor of three in pigs.
- The new studies suggest that the MRLs for skin/fat of chickens and for muscle of pigs should be higher than those recommended at the 54th meeting of the Committee. The MRLs for fat could be maintained for both species,

provided that a separate MRL was recommended for skin with adhering fat in pigs in order to reflect the high concentrations found in the skin of that species.

- For the benefit of residue control programmes, it would be appropriate to harmonize the MRLs in chickens and pigs as far as possible.
- The temporary MRLs for tissues of cattle and sheep should be withdrawn, as the requested information was not provided.

On this basis the Committee recommended the following MRLs:

Species	MRL [µg/kg]				
	Liver	Kidney	Muscle	Fat[a]	Milk
Cattle	-	-	-	-	150
Pigs	500	1500	200	100	
Chickens	500	500	200	100	

[a] The MRLs for fat that were recommended at the 54th meeting of the Committee were maintained. A separate MRL of 300 µg/kg for skin with adhering fat in pigs was recommended in order to reflect the high concentrations found in the skin of pigs. For consistency, an MRL of 300 µg/kg for skin with adhering fat in chickens was also recommended.

Daily consumption of 100 g liver, 50 g kidney, 300 g muscle and 50 g fat of pigs and 1500 g of cows milk would result in a Theoretical Maximum Daily Intake of 415 µg per person per day or 23% of the ADI for a person with a body weight of 60 kg.

The temporary MRLs for edible tissues of cattle and sheep were not retained.

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