THIAMPHENICOL

First draft prepared by
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ADDENDUM
to the thiamphenicol residue monograph
prepared by the 47th meeting of the Committee and published in
FAO Food and Nutrition Paper 41/9, Rome 1996.

INTRODUCTION

The Committee has previously considered the antimicrobial agent thiamphenocol at the forty-seventh meeting. At that meeting the Committee recommended temporary MRLs of 40 μg/kg for poultry and cattle muscle, liver, kidney and fat, expessed as the parent drug. MRLs were not recommended for eggs because of unacceptably high thiamphenicol residues. No MRLs were proposed for cattle milk or pigs because no data were supplied on total residues in milk and the data supplied for pigs were considered insufficient to allow a recommendation for MRLs.

In reaching this decision, based on the data package supllied by the sponsor, the 47th Committee considered the following factors:

- A temporary ADI of 0-6 μg/kg BW was recommended based on a toxicological endpoint, that corresponds to 300 μg per day for a 60 kg person.
- There was a dearth of data to determine the percentage of marker residue to total residue in the edible tissues of target species.
- The limits of quantification and detection of available analytical methods were 0.02 mg/kg and 0.01 mg/kg, respectively.

- There was a a lack of depletion studies in target animals extending to periods beyond the withdrwal times at maximum recommended dosage.

The Committee requested that the following additional information be required for evaluation in 1999:

- Detailed reports of the carcinogenicity study in rats on which the summary report was available at the 47th meeting and the range-finding study used to establish dose levels in that study.

- Residue depletion studies with radiolabeled and unlabeled thiamphenicol for identification of the marker residue and target tissues in non-ruminant cattle, poultry and pigs.

The evidence on which the Committee made its determination has been reported previously. (FAO, 1997). This monograph reviews data submitted by the sponsor that addresses the second of the Committee's requests for new information. In addition, new material supplied by the sponsor on pharmacokinetics and residue depletion in fish and sheep is also included. However, no radiolabeled studies were reported, as requested by the Committee.

IDENTITY

Chemical name: D-d-threo-2-dichloroacetamido-1-(4-methylsulfonylphenyl)-1,3-propanediol (IUPAC) [R-(R*.R*)]-2,2-dichloro-N-[2-hydroxy-1-(hydroxymethyl)-2-(4-(methylsulfonyl) phenyl]ethyl]acetamide (CAS)

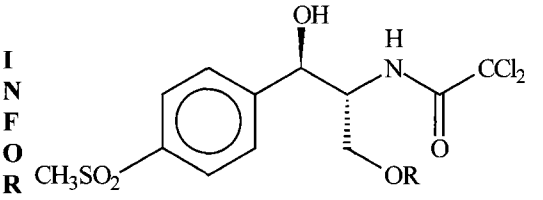
Molecular formula: $C_{12}H_{15}Cl_2NO_3S$

Molecular weight: 356.23

Chemical structure:

OTHER

INFORM



R = H
Thiamphenicol

R = $COCH_2NH_2$ HCl
Thiamphenicol glycinate hydrochloride

ATION ON IDENTITY AND PROPERTIES

Appearance: White crystalline powder

Melting point: 164-166^{0}C

Optical rotation: $[\alpha]_D^{25^\circ} = +12.9^0$ (ethanol)

UV spectrum (max): 224, 266, 274 nm (ε, 13,700,800,700)

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

General

Thiamphenicol is used for the treatment of certain bacterial diseases in cattle, pigs, poultry and fish. The product is usually used as an oral preparation, but is not suitable for the treatment of ruminating cattle.

Dosage

Thiamphenicol is used for oral administration and thiamphenicol glycine hydrochloride is utilised in formulations for parenteral use.

METABOLISM AND PHARMACOKINETIC STUDIES

Pigs

In a study which complied with GLP (Redgrave *et al.*, 1991), sixteen pigs weighing 15-22 kg and about 7 weeks old were fed thiamphenicol in the diet twice a day for five consecutive days. Each dose was approximately 30 mg/kg BW and three untreated animals acted as controls. Blood samples were taken immediately prior to dosing and at periods during the next 10 days. Results, which appear in Table 1, show that maximum mean plasma levels of 1.28 mg/L were attained 8 h after the first administration. After the withdrawal of treatment, plasma concentrations declined to close to or below, the LOD of the assay method after five days.

In another non-GLP study in pigs (Fornasini, 1992), thiamphenicol was orally administered twice daily to 15 pigs of mean weight 30 kg, randomly divided into three groups of five, and dosed at 10, 15 and 20 mg/kg BW for five consecutive days. The plasma values for thiamphenicol and thiamphenicol glucuronide were determined by GC using electron capture detection. The results of this study, previously summarised (FAO, 1997), are important in that they showed that glucuronide formation is an important route of elimination of thiamphenicol in pigs. Indeed, the mean plasma glucuronide concentrations at all time points after the last dose were higher than the concentrations of free

thiamphenicol. However, whereas plasma concentrations of thiamphenicol were dose related, those of thiamphenicol glucuronide were not.

Table 1. Mean plasma concentrations of thiamphenicol in pigs fed a diet containing 900mg/kg of thiamphenicol (approximately 30 mg/kg BW) twice daily for five consecutive days

Study day (withdrawal day)	Time (h)	Thiamphenicol (mg/L)		Study day (withdrawal day)	Time (h)	Thiamphenicol (mg/L)	
		Mean (n = 6)	Range			Mean (n = 6)	Range
1	0	ND	-	6 (1)	8	0.05	0.03 – 0.11
	2	1.25	0.93 – 1.67		12	0.04	0.02 – 0.06
	4	1.25	0.81 – 1.85		16	0.02	ND – 0.04
	6	0.85	0.57 – 1.47		20	<0.02	ND – 0.02
	8	1.28	0.85 – 1.65	7 (2)	24	0.02	0.02 – 0.03
	16	0.80	0.57 – 1.51		12	<0.02	ND – 0.03
2	24	0.24	0.15 – 0.58	8 (3)	24	~0.01	ND – 0.03
3	24	0.34	0.14 – 1.12		12	~0.01	ND – 0.02
4	24	0.31	0.17 – 0.88	9 (4)	24	ND	ND
5	24	0.39	0.14 – 1.14		12	~0.01	ND – 0.04
6 (1)	24	0.22	0.12 – 0.48	10 (5)	24	ND	ND
	4	0.08	0.05 – 0.17				

In a more recent study, in conformance with GLP, four castrated male pigs weighing 100-120 kg were concurrently treated orally with 30 mg/kg BW and IV with 10 mg/kg BW thiamphenicol (Villa and Brightwell, 1997a,b). Blood samples were collected in the first 24 h and urine was collected to 48 h post dosing. All samples were measured by a validated HPLC method with a LOQ of 21 µg/L in plasma and 210 µg/L in urine. Results are shown in Table 2. After oral administration, the $t_{1/2}$ was 3.88 h and 4.57 h and AUC was 23.96 mg x h/L and 91.04 mg x h/L for unconjugated and total thiamphenicol, respectively. After IV administration, the $t_{1/2}$ was 3.43 h and 4.64 h and AUC was 12.64 mg x h/L and 23.29 mg x h/L for unconjugated and total thiamphenicol, respectively. In urine, highest concentrations of total thiamphenicol occurred 4 h after oral dosing and ranged between 610-723 mg/L while, after IV dosing, maximum urine concentrations also occurred after 4 h with a range of 363-1136 mg/L.

Table 2. Mean plasma concentrations of thiamphenicol in pigs administered a single oral dose of 30 mg/kg BW or a single IV dose of 10 mg/kg BW

Time (h)	Thiamphenicol (TAP) conc. (mg/L) after oral dosing			Time (h)	Thiamphenicol conc. (mg/L) after IV dosing		
	Free TAP (SD)	Glucuronide (SD)	Total TAP (SD)		Free TAP (SD)	Glucuronide (SD)	Total TAP (SD)
0.25	1.72 (0.43)	4.73 (2.67)	6.45 (3.09)	5 (min)	36.46(10.60)	12.17 (9.28)	48.64 (2.51)
0.5	2.88 (0.47)	6.31(1.64)	9.20 (1.98)	10 (min)	20.31(7.10)	14.57 (2.40)	34.88 (6.23)
1	3.08 (0.94)	7.11(1.12)	10.20 (2.01)	20 (min)	11.96 (2.53)	8.57 (3.87)	20.53 (1.77)
2	2.80 (0.61)	6.27 (2.30)	9.08 (2.23)	45 (min)	3.23 (1.38)	4.60 (2.44)	7.84 (1.03)
3	2.15 (0.60)	4.84 (0.80)	7.00 (1.17)	1	2.20 (0.59)	1.70 (1.28)	3.90 (1.03)
4	2.06 (1.530	7.52 (1.14)	9.59 (1.36)	2	0.85 (0.37)	0.75 (0.58)	1.61(0.55)
6	1.53 (0.43)	4.33 (1.06)	5.87 (1.45)	3	0.28 (0.10)	0.38 (0.09)	0.66 (0.06)
8	0.83 (0.24)	2.82 (1.21)	3.66 (1.35)	4	1.51(1.04)	0.39 (0.36)	0.27 (0.06)
12	0.35 (0.10)	1.16 (0.65)	1.51 (0.75)	8	0.05 (0.03)	0.10 (0.06)	0.16 (0.06)
24	0.35 (0.11)	0.85 (0.39)	1.21 (0.48)	12	0.02 (0.005)	0.07 (0.04)	0.10 (0.04)
				24	0.005(0.002)	0.02 (0.02)	0.03 (0.02)

Fish

Pharmacokinetic studies of the use of thiamphenicol in yellowtail have been reviewed (Eisai Co Ltd, 1997a). Thiamphenicol was administered as a single dose, mixed in feed, to fish weighing 190g and reared at 28°C, at 100 mg/kg BW. Blood was collected, using 7 fish for each time-point, at 3, 6, 12, 24 and 48h. Peak thiamphenicol concentrations, as measured by a colorimetric method, occurred at 3-6 h with a C_{max} 9.4-12.1 mg/L. No drug could be detected in blood after 48 h but high levels were detected in bile at 24 h, supporting the hypothesis that bialy excretion is the major elimination pathway in fish. No metabolites were identified.

The bioavailability of thiamphenicol in seabass (*Dicentrarchus labrax*), reared at 15 ± 2°C after a single dose and also after dosing for five days has been studied. Thiamphenicol was administered in the feed at 15 and 30 mg/kg/day, the fish being force-fed for single dose studies and in the feed for multiple dose studies. Adsorption of the drug from medicated feed was slow and incomplete in comparison with the forced feeding study ($AUC_{0\text{-}72h}$ ≈ 39.34 mg h/L compared to 197.39 mg h/L at the higher dose). Thiamphenicol concentrations in blood declined rapidly and were below the LOQ of the analytical method (50 µg/L) 7 days after the last treatment.

RESIDUE DEPLETION STUDIES

Pigs

In a recent GLP-compliant residue depletion study in pigs, 25 crossbreds weighing from 25-30 kg each were randomly divided into 5 equal groups (Villa and Brightwell, 1997a). Four groups were fed a thiamphenicol-containing diet such that each pig consumed 30 mg/kg/day BW of drug for 5 days while the last group (controls) received standard non-medicated diet. Groups were treated at different times so that all animals could be sacrificed together after withdrawal of drug, which occurred at 5,10,16 and 18 days for the respective groups. All tissues were analysed for the marker residue, thiamphenicol, by a validated HPLC method with an LOQ and LOD of 21 µg/kg and 5 µg/kg, respectively (Villa and Brightwell, 1997b). The results are shown in Table 3. Thiamphenicol was not present in muscle, except for two animals at day 10. In liver, mean residues of thiamphenicol were 27.35 µg/kg at day 18 while, at the same time point, kidney and skin values were 39.14 and 94.6 µg/kg, respectively. It should be noted that %CV were very large at several time points, particularly for kidney.

In a second GLP-compliant residue depletion study, 32 crossbred pigs weighing from 45-65.2 kg each were divided into 8 groups, each containing two males and two females (Luperi and Villa 1998a). Seven groups were dosed IM with 30 mg/kg/day BW thiamphenicol for 5 days while the last group acted as a control. Groups were sacrificed at 8 hours, and 1,4,8, 15, 21, and 28 days after the last administration of drug, respectively. Samples of muscle, muscle injection site, liver, kidney, visceral fat and skin/fat were taken from each animal while lung samples were also taken from animals in the 8 hour and one day groups. All tissues were analysed for thiamphenicol, by the same validated HPLC method used in the previous study (Villa and Brightwell, 1997b). The results are shown in Table 4. Thiamphenicol concentrations decreased to below 50 µg/kg in all tissues investigated 8 days after the last administration. After 28 days, thiamphenicol residues could only be detected in injection sit muscle at levels above the LOQ.

In neither of the two studies, summarised in Tables 3 and 4, were investigations undertaken to determine if thiamphenicol glucuronide was a major metabolite in any tissue and, if so, how much was present in that tissue. This was despite the fact that pharmacokinetic studies (*vide supra*) had demonstrated that the glucuronide conjugate of thiamphenicol represented the dominant proportion of thiamphenicol in plasma and a significant metabolite in the urine of pigs after oral dosing. The glucuronide conjugate could represent a significant proportion of total metabolites in any tissue. The 47th meeting of the JEFCA Committee had considered this possibility in requesting the sponsor to provide new residue depletion studies with radiolabelled and unlabeled thiamphenicol for identification of the marker residue and target tissues in non-ruminant cattle, poultry and pigs. The studies discussed above (Villa and Brightwell, 1997a; Luperi and Villa 1998a) neither unambiguously identifies the thiamphenicol as the correct marker residue in all pig tissues nor gives any information of the ratios of thiamphenicol to the total residues in pig tissue at any time point.

Table 3. Mean tissue concentrations (µg/kg) of thiamphenicol in the tissues of pigs following oral administration of 30 mg /kg /day BW (n=5) for 5 consecutive days.

Days after withdrawal		Thiamphenicol concentration (µg/kg)				
		Muscle	Liver	Kidney	Fat	Skin
5	Mean (%CV)	ND	56.3 (50.4)	534.6 (157.6)	<LOQ	228.8 (57.4)
	Range	ND	29.2-96.2	18.7-1975	LOD-<LOQ	101.6-403.0
10	Mean (%CV)	10. 6 (137.5)*	38. 5(40.74)	127.7 (64.4)*	11.3 (64.3)*	120.2 (34.8)
	Range	ND-28.3	21.7-62.5	15.2-236.6	LOD-23.9	57.3-167.0
16	Mean (%CV)	ND	22.5 (57.1)*	83.5 (78.7)*	LOD-LOQ	153.1 (38.9)
	Range	ND	ND-30.9	<LOQ-173.2	<LOQ-<LOQ	93.0-230.3
18	Mean (%CV)	ND	27.4 (11.4)	39.1 (159.2)*	~LOD	94.6 (24.8)
	Range	ND	24.9-32.6	~LOD -150.3	ND-<LOQ	67.4-129.9

* estimated value only because some individual values were below the quantification range of the analytical method.
ND = not detected; LOD = 5 µg/kg; LOQ = 21 µg/kg

Table 4. Mean tissue concentrations (μg/kg) of thiamphenicol in the tissues of pigs following IM administration of 30 mg /kg /day BW (n=4) for 5 consecutive days.

Days after withdrawal		Thiamphenicol concentration (μg/kg)					
		Muscle	**Liver**	**Kidney**	**Visceral Fat**	**Skin/Fat**	**Lung**
8 (hours)	Mean (%CV)	1756 (8.2)#	642 (28.1)	6675 (20.3)#	552.9(44.0)	991.1(26.3)#	2240 (28)#
	Range	1570-1910	459-806	5240-8510	265-857	647-1240	1430-2820
1	Mean (%CV)	389.5 (49.5)	111.2 (127.9)	1648 (69.9)#	84.1 (20.5)	203.7 (60.0)	529.1 (38.8)
	Range	151.4-585.0	14.3-322.4	401.1-3090	61.6-103.5	120.2-384.8	326.4-814.8
4	Mean (%CV)	10.8 (58.1)*	LOD	55.0 (66.2)*	22.6 (76.9)*	32.3 (85.2)*	-
	Range	<LOQ-20.0	<LOD-<LOQ	<LOQ-104.9	ND-41.8	<LOQ-72.9	-
8	Mean (%CV)	LOD-LOQ	<LOD	24.0 (78.0)*	<LOQ	LOD-LOQ	-
	Range	~LOD-<LOQ	<LOD-LOD	~LOD-47.18	ND-22.3	<LOQ-32.9	-
15	Mean (%CV)	~LOD-LOQ	ND	16.5 (56.8)*	ND	<LOD	-
	Range	~LOD-LOQ	ND	<LOQ-28.2	ND	ND-~LOD	-
21	Mean (%CV)	~LOD	ND	14.2 (92.7)*	ND	ND	-
	Range	<LOD-LOD	ND	~LOD-30.0	ND	ND	-
28	Mean (%CV)	ND	ND	ND	ND	ND	-
	Range	ND	ND	ND	ND	ND	-

* estimated value only because some individual values were below the quantification range of the analytical method
\# estimated value only because some individual values were above the validation range of the analytical method
ND = not detected ; LOD = 5 μg/kg; LOQ = 21 μg/kg

Sheep

A GLP-compliant residue depletion study in sheep has recently been reported (Luperi and Villa 1998a). Sixteen crossbred sheep, weighing from 55.0-73.7 kg for males and 38.6-56.0 kg for females, were divided into 4 groups, each containing two males and two females. Each group was dosed IM with 30 mg/kg/day BW thiamphenicol for 5 consecutive days. Groups were sacrificed at 4, 8, 12, and 16 days after the last administration of drug, respectively. Samples of muscle, muscle injection site, liver, kidney, and abdominal fat, taken from each animal, were analysed for thiamphenicol, by a validated HPLC method with an LOQ and LOD of 21 μg/kg and 2.4-5.2 μg/kg, respectively (Villa and Brightwell, 1997b). The results are shown in Table 5. Thiamphenicol was not present in muscle or liver, and in kidney and fat values were 43.2 and 342.5 μg/kg, respectively at day 4. No residues could be quantified in any tissue at all later time points

This study did not attempt to detect or quantify the presence of thiamphenicol glucuronide. There is no data that establishes that thiamphenicol is the correct marker residue for sheep tissues, nor is there data that enables the determination of the relationship between unconjugated thiamphenicol and total residues in any tissue.

Table 5. Mean tissue concentrations (µg/kg) of thiamphenicol in the tissues of sheep following IM administration of 30 mg /kg /day BW (n=4) for 5 consecutive days.

Days after withdrawal		Thiamphenicol concentration (µg/kg)			
		Muscle	Liver	Kidney	Fat
4	Mean (%CV)	<LOD	ND	40.2 (129.6)	342.5 (112.8)
	Range	ND-LOD	ND	ND-116.9	79.1-905.8
8	Mean (%CV)	<LOD	ND	ND	~LOD
	Range	<LOD	ND	ND	ND-<LOQ
12	Mean (%CV)	ND	ND	ND	~LOD
	Range	ND	ND	ND	ND-<LOQ
16	Mean (%CV)	ND	ND	ND	ND
	Range	ND	ND	ND	ND

* estimated value only because some individual values were below the quantification range of the analytical method. ND = not detected; LOD = 5 µg/kg; LOQ = 21 µg/kg

Fish

Thiamphenicol was administered, mixed in feed, to yellowtail fish weighing 210g and reared at 23.0-27.5°C at doses of 45 (recommended dose) and 90 mg/kg/day BW for 14 days in a non-GLP compliant study (Eisai Co Ltd, 1997b). Muscle, liver, kidney and skin with fat were collected on day 10 of administration and at 0, 3, 7, 10, 14 21 and 28 days after the finish of treatment. Residue levels of free thiamphenicol were highest in liver, followed by kidney liver and skin, but were very low in muscle. Residues fell below the detection limit of the GC analytical method used (20 µg/kg) 3 days after cessation of treatment.

In a recent study (Della Rocca *et al.*, 1997a), which was not performed to GLP requirements, thiamphenicol was fed to seabass (*Dicentrarchus labrax*), weighing 140-150g and reared at 18-28°C at 40 mg/kg/day BW for 5 days. This is both the recommended dosing rate and time of administration. Muscle, liver, skin and vertebrae were collected from groups of 10 fish on days 2 and 4 of administration and at 1, 2, 3, 5, 7 and 10 days after the finish of treatment and thiamphenicol concentrations determined by HPLC. Results of the study are summarised in Table 6. Residue levels of free thiamphenicol were highest in liver, followed by muscle and skin. Residues fell below the detection limit of the HPLC analytical method used (20 - 100 µg/kg) 5 days after cessation of treatment.

Table 6. Mean tissue concentrations (µg/kg) of thiamphenicol in the tissues of seabass (*Dicentrarchus labrax*) following oral administration of 40 mg /kg /day BW (n=10) for 5 consecutive days.

Day of sampling	Thiamphenicol concentration (µg/kg)							
	Muscle		Liver		Skin		Vertebrae	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
2 During dosing	1270	920	6360	3450	650	360	440	190
4 During dosing	3010	1180	6450	6020	1140	420	780	290
1 After dosing	1830	760	6380	3520	890	420	160	50
2 After dosing	60	30	1500	810	90	50	120	70
3 After dosing	28	30	410	230	<50		90	30
5 After dosing	<20		<100		<50		<50	

LOQ = 20 µg/kg in muscle, 50 µg/kg in skin and vertebrae and 100 µg/kg in liver

In a second related study (Della Rocca *et al.*, 1997b), which was not performed to GLP requirements, thiamphenicol was fed to seabream (*Spartus aurata*), weighing 100-120g and reared at 18-28°C at 40 mg/kg/day BW for 5 days. This is both the recommended dosing rate and time of administration. Muscle, liver, skin and vertebrae were collected from groups of 10 fish on days 2 and 4 of administration and at 1, 2, 3 and 5 days after the cessation of treatment and thiamphenicol concentrations determined by HPLC. Results of the study are summarised in Table 7. Residue levels of free thiamphenicol were highest in liver, followed by muscle and skin. Residues fell below the detection limit of the HPLC analytical method used (20 - 100 µg/kg) 5 days after cessation of treatment.

Table 7. Mean tissue concentrations (µg/kg) of thiamphenicol in the tissues of seabream (*Spartus aurata*) following oral administration of 40 mg /kg /day BW (n=10) for 5 consecutive days.

Day of sampling	Thiamphenicol concentration (µg/kg)							
	Muscle		Liver		Skin		Vertebrae	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
2 During dosing	1160	1070	8500	5400	2640	1730	220	190
4 During dosing	1970	910	6900	3410	2520	2540	530	340
1 After dosing	1470	810	3890	1740	700	370	380	230
2 After dosing	240	140	380	100	180	60	120	70
3 After dosing	30	-	<100		<50		80	20
5 After dosing	<20		<100		<50		<50	

LOQ = 20 µg/kg in muscle, 50 µg/kg in skin and vertebrae and 100 µg/kg in liver

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

A number of methods for the analysis of thiamphenicol residues have been reported which were not previously discussed in the monograph from the 47th meeting of the Committee (FAO, 1997). These are discussed below.

An HPLC method for the detection and quantification of residues of free thiamphenicol in the plasma, urine and tissues of pigs has been validated in accordance with GLP regulations (Villa and Brightwell, 1997b). Tissue is homogenised, extracted with ethyl acetate and the ethyl acetate extract washed with aqueous sodium chloride. The ethyl acetate is removed in a stream of nitrogen, the residue dissolved in water and extracted with hexane and the final aqueous layer injected onto a reverse phase HPLC column. Thiamphenicol is determined by elution with methanol-water and detection by UV at 224 nm. For kidney and urine samples, a florisil clean-up stage is inserted after evaporation of the ethyl acetate. Also, the elution solvent is modified when dealing with these samples. The method has been validated for a LOQ of 21 µg/kg and a LOD of 5 µg/kg in all matrices except urine, with a CV below 5% for all matrices except liver where the CV was 8%. However, quantitative results have been quoted using this method that are well below the stated LOQ, and even below the stated LOD (Villa and Brightwell, 1997a). The accuracy and precision of the method at these values was not stated although both quantification values and coefficients of variation were provided to two decimal places. For urine, the LOQ was 210 µg/L and a LOD of 25 µg/L.

The method has also been used to determine the sum of thiamphenicol and thiamphenicol glucuronide in plasma and urine samples by the introduction of a gluronidase deconjugation step at the beginning of the procedure. This work was not extended to the determination of thiamphenicol glucuronide in tissue samples.

This same HPLC procedure has also been validated for determination of thiamphenicol in sheep plasma, urine and tissues (Villa and Brightwell, 1998).

A HPLC procedure for the determination of thiamphenicol in fish tissues has not been validated in accordance with GLP. The LOQs obtained for different tissues were 20 µg/kg in muscle, 50 µg/kg in skin and vertebrae and 100 µg/kg in liver (Anfossi, 1998)

APPRAISAL

At the 47th meeting The Committee requested that residue depletion studies with radiolabelled and unlabelled thiamphenicol for identification of the marker residue and target tissues in non-ruminant cattle, poultry and pigs. The data that was submitted by the sponsor only partially addressed the Committee's requests for new information. The sponsor also provided unsolicited information on pharmacokinetics and residue depletion in fish and sheep. However, no radiolabelled studies were reported as requested by the Committee.

The 47th meeting of the JEFCA Committee requested the sponsor to provide new residue depletion studies with radiolabelled and unlabelled thiamphenicol for identification of the marker residue and target tissues in non-ruminant cattle, poultry and pigs. The data provided neither unambiguously identifies thiamphenicol as the correct marker residue in all pig tissues nor provides any information of the ratios of thiamphenicol to the total residues in pig tissue at any time point. This was despite the fact that pharmacokinetic studies have demonstrated that the thiamphenicol glucuronide conjugate represented the dominant proportion of thiamphenicol in plasma and a significant metabolite in the urine of pigs after oral dosing.

Furthermore, no residue study undertaken has attempted either to detect or quantify the presence of thiamphenicol glucuronide as a portion of the total residues. The major thiamphenicol metabolites in tissues of any food animal or fish species are unknown and the occurrence of conjugated metabolites of thiamphenicol in edible tissues has not been investigated. The possibility of extensive metabolism of thiamphenicol in liver tissues cannot be disregarded. However, there is no data that allow the determination of the ratio of marker residue to total residues in any species. It is recognised that thiamphenicol glucuronide was not microbiologically active but could, on human ingestion, be converted to the microbiologically active parent drug.

Due to the lack of information on tissue metabolites, the Committee recommends that the marker residue for thiamphenicol should be the sum of thiamphenicol and thiamphenicol conjugates, measured as thiamphenicol. This marker residue will apply to temporary MRLs until further work has been conducted to establish the metabolite distribution in edible tissue.

Because the sponsor did not supply the data requested by the 47th Committee to support the use of thiamphenicol in cattle and chickens, the temporary MRLs previously recommended for these species are withdrawn.

The Committee requests the sponsor to provide for consideration by the Committee in 2002:

1. A satisfactory depletion study in pigs to determine the relationship between free thiamphenicol, thiamphenicol conjugates and total residues in all tissues.
2. A validated analytical method for use in all animal tissues, which incorporates an enzymatic hydrolysis step that will allow the determination of thiamphenicol and thiamphenicol conjugates as as free thiamphenicol.

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