



COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

THIAMPHENICOL (Extension to pigs and extrapolation to all food producing species)

SUMMARY REPORT (6)

1. Thiamphenicol (CAS: 15318-45-3) is a broad-spectrum antibiotic closely related to chloramphenicol: the chemical structure of thiamphenicol differs from that of chloramphenicol in having a sulpho-group instead of a nitro-group. It is active against both Gram-negative and Gram-positive bacteria, and is especially active on anaerobes.
2. Thiamphenicol is used for the treatment and control of respiratory and intestinal infections in cattle and poultry; the routes of administration are oral or intramuscular. However, the substance is also intended for intramammary administration in both lactating and dry cows and for intrauterine administration in cows. Thiamphenicol is used for the treatment of pigs against respiratory and intestinal disease with a recommended dose of 30 mg/kg bw orally, intramuscularly or intravenously for up to 5 days.

Currently, thiamphenicol is included in Annex I of Council Regulation EEC No 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Thiamphenicol	Thiamphenicol	Bovine	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg	Muscle Fat Liver Kidney Milk	
		Chicken	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg	Muscle Skin+fat Liver Kidney	Not for use in animals from which eggs are produced for human consumption

and in Annex III of Council Regulation (EEC) No 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Thiamphenicol	Thiamphenicol	Porcine	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg	Muscle Skin+fat Liver Kidney	Provisional MRLs expire on 1.1.2007

The information requested for the establishment of final MRL for thiamphenicol in pigs has now been provided. The CVMP having evaluated the response to the List of Questions has considered that the provisional MRLs can be confirmed as final, the summary of the assessment is provided below.

3. At this occasion, the CVMP has also taken into account the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-Final) that allows for an extrapolation of MRLs to all food producing species, where identical or slightly different MRLs (i.e. MRL values normally in the same order of magnitude) have been set in cattle (or sheep), pigs and chicken (poultry).
4. The existing thiamphenicol MRLs for bovine and chicken and the proposed final pig MRLs are identical and so it would be possible to recommend extension of the MRLs in such a way that the same MRL values apply to all food producing species. Analytical methods for monitoring residues of thiamphenicol in bovine, porcine and chicken tissues and in bovine milk are available.
5. In setting the ADI in the original assessment of thiamphenicol, the data summarised in the paragraphs below were considered.
6. Thiamphenicol is essentially a bacteriostatic antibiotic: it acts by binding to the 50-S subunits of the 70-S ribosomes, thus blocking peptidyl transferase and resulting in the inhibition of bacterial protein synthesis.

No information is available on the possible secondary pharmacological effects of thiamphenicol on organ and system functions.

7. Following either oral or parenteral administration, thiamphenicol is well absorbed and rapidly and extensively distributed to the tissues in rats, guinea pigs and dogs.

The compound is transferred through the placenta, the blood-brain barrier and into the milk.

In a radiolabelled study in the rat, 97% of a single oral 30 mg/kg bw dose was eliminated within 48 hours with approximately 65% of the dose being excreted in the urine. In the bile 3.4% of the administered dose appeared unchanged and 12% as conjugated products after 4 hours; more than 30% of the dose was excreted in the faeces within 75 hours. Thiamphenicol was excreted in urine and faeces almost entirely in the unchanged form.

In the rat the substance was widely distributed in almost all tissues, except for brain; the tissues containing the highest radiolabelled residues were the liver and kidney. The liver was the only tissue to present measurable radioactivity as long as 72 hours after administration. No significant accumulation occurred in body fat as compared to other tissues.

Unlike chloramphenicol, thiamphenicol may not be an optimal substrate for the hepatic microsomal enzyme glucuronyl transferase. In rabbits and rats, more than 95% of the administered dose is excreted unchanged. A higher level of glucuronidation occurs in guinea-pigs and pigs. About 30% of thiamphenicol undergoes glucuronidation when tested on pig hepatocytes *in vitro*.

Pharmacokinetic studies in humans show rapid absorption, distribution and elimination following oral treatment, with an elimination half-life of 2 to 3 hours. Diffusion into tissues is favoured by modest (less than or equal to 10%) binding to plasma proteins. Little conjugation with glucuronic acid occurs in the liver. About 55% of the administered dose is excreted in the urine as unchanged parent compound, with variable but generally low amounts of deacyl- and glucuronide conjugates; overall urinary excretion accounts for more than 50 to 70% of the administered dose.

The pharmacokinetic profile in plasma and urine was investigated in calves receiving a single intramuscular dose of 25 mg/kg bw of thiamphenicol. The peak plasma level occurred 1 to 1.5 hours after administration. The ranges of the plasma pharmacokinetic values were as follows: C_{max} 8.5 to 18.7 µg/ml; plasma elimination half-life 2 to 3 hours; volume of distribution 590-1115.4 ml/kg; clearance 346.1 to 375 ml/hour/kg. The total urinary recovery (0 to 96 hours) ranged from 22 to 59%.

In calves administered orally 50 mg/kg bw of thiamphenicol, subdivided into two daily administrations, for 4 days, the average plasma concentrations fell from 7.1 µg/ml 6 hours after the last treatment to 2.25 µg/ml after 24 hours down to 0.54 µg/ml after 34 hours.

The pharmacokinetic profile was investigated in dairy cows treated intramuscularly with a total daily thiamphenicol dose of 30 mg/kg bw, divided into two 15 mg/kg bw injections, for five days. The average plasma half-life of thiamphenicol was slightly more than 2 hours. The observed AUC_{0-6h} averaged 46 mg/h/ml and was 86% of the estimated total AUC (53.79 mg/h/ml). The apparent plasma clearance and the apparent volume of distribution were 290 ml/hour/kg and 860 ml/kg, respectively.

8. In a ^{14}C -radiolabelled study broiler chickens were administered an oral single thiamphenicol dose of 25 mg/kg bw. Plasma levels peaked at 1 to 2 hours post-dosing; the average values were 6.59 and 4.58 µg/ml in males and females respectively. The AUC_{0-24h} was 0.97 µg/h/ml. About 90% of the dose was eliminated unmodified within 24 hours through both bile and urine; 5 days after treatment less than 1% of the dose was retained in the carcass and gastrointestinal tract.

In a further trial 48 broiler chickens were treated orally with 50 mg/kg bw ^{14}C -thiamphenicol subdivided into two daily doses for 5 days. HPLC analysis showed that approximately 95% of the radioactivity was excreted as unmodified thiamphenicol within 48 to 72 hours. A two-phase depletion of tissue and bile concentrations was observed, with a rapid decrease (approximately 10-fold in bile and 2-3-fold in tissues) from 6 to 24 hours after the end of treatment, and a slower depletion rate up to 120 hours (last sampling time). Mean bile concentrations were 37.35, 3.59, 0.34 and 0.12 µg equivalent/ml after 6 hours, 1, 3 and 5 days following the last treatment, respectively.

9. Acute oral toxicity is low, the LD50 for thiamphenicol being higher than 5000 mg/kg in both rats and mice.
10. In a 4-week oral study on Large White Hybrid pigs, reduced weight gain and food consumption were observed at and above 50 mg/kg bw, while decreased urinary pH was detected even at the lowest dose level tested, 25 mg/kg bw.

In a 90-day oral study on Sprague-Dawley rats, decreased erythrocyte and white blood cell counts were observed at and above 45 mg/kg bw; the changes partly reversed following an 8-week recovery period. The NOEL was 30 mg/kg bw.

In a 13-week study, published in 1997, four groups of F344 rats (12/sex) were exposed through the drinking water to 0, 125, 250 and 500 mg/l of thiamphenicol, equal to 0, 9.0, 20.8 and 38.6 mg/kg bw, respectively. Adverse effects were observed down to 20.8 mg/kg bw, including reduced weight gain in both sexes; decreased erythrocyte count and blood haemoglobin; increased relative liver and kidney weights and decreased relative thymus weight; reduced bone marrow erythropoiesis; testicular lesions (vacuolation of germinal epithelium, spermatogranulomas, reduced sperm in the epididymis). No effects on organs or tissues were observed at 9.0 mg/kg bw, besides a dose-related enlargement of caecum, which is a usual side-effect in rodents following prolonged oral administration of antibiotics. However, slight but dose-related haematological (increased mean red cell volume, reduced platelet concentration) and biochemical (reduced serum total protein and cholesterol concentrations in females) changes were observed even at 9.0 mg/kg bw.

In a 6-month oral study on beagle dogs dosed with 0, 15, 30 or 60 mg/kg bw/day, tremors, lethargy and reduced weight gain were observed at the top dose level. Increased relative liver weight, decreased erythrocyte count and haematocrit values, reduced cellularity of bone marrow and focal testicular atrophy were observed down to 30 mg/kg bw. No effects, including bone marrow alterations, were observed at the end of a 2-month recovery period. The NOEL was 15 mg/kg bw.

11. A battery of genotoxicity tests were performed, including *in vitro* bacterial mutagenicity assay, *in vitro* assay for gene mutation in mammalian cells, *in vitro* assay for chromosomal aberrations on human lymphocytes, *in vitro* assay for DNA repair on rat hepatocytes, and *in vivo* oral micronucleus test in the mouse.

All tests gave negative results; therefore thiamphenicol was considered non-genotoxic.

12. The summary report of a GLP carcinogenicity study in Fischer 344 rats was made available to JECFA. No tumour increases were observed; however, the lack of detailed data does not allow for an independent assessment.

There was no evidence from the genotoxicity data that thiamphenicol may possess a carcinogenic potential.

13. In a pre-GLP one-generation reproduction study on rats, reduced spermatogenesis was observed down to the lowest dose level tested, 120 mg/kg bw.

Thiamphenicol did not elicit teratogenic effects in the rat; increased resorption rate and peri- and postnatal mortality were observed with concurrent maternal toxicity. There was experimental *in vitro* evidence that thiamphenicol may impair mitochondrial respiration in rat embryos. The NOEL for both maternal and developmental toxicity in rats was 40 mg/kg bw.

In an embryotoxicity/foetotoxicity study on the rabbit, maternal toxicity was observed down to the lowest level tested (1.25 mg/kg bw). No teratogenic effects were induced up to the top dose level of 5.0 mg/kg bw. Reduced foetal weight was observed with a NOEL for foetal effects of 1.25 mg/kg bw.

14. No original studies on the effects on the intestinal gut flora were provided.

A review of the available published literature showed that for most aerobic strains the MIC₅₀ was more than or equal to 32 µg/ml.

On the other hand, gram-positive anaerobe bacteria are especially sensitive to thiamphenicol. The most sensitive species were *Actinomyces*, *Propionibacterium*, and *Fusobacterium*, with a MIC₅₀ (most sensitive value) of 0.5 µg/ml. Since more than 10 strains were tested for such species, and *Fusobacterium* is considered as one of the most relevant microorganisms for the human gut flora, this value was considered as an appropriate basis for the microbiological ADI.

Cross-resistance has been reported between thiamphenicol and chloramphenicol. However, some chloramphenicol-resistant strains are susceptible to thiamphenicol.

No increase of drug-resistant strains was observed in mice following a 35-day dietary exposure equivalent to 4 mg/kg bw of thiamphenicol.

15. Limited data show that the NOELs for microorganisms utilised in food industry were as follows: *Lactobacillus acidophilus* more than or equal to 16 µg/ml; *Lactobacillus delbrueckii* (bulgaricus) 4 µg/ml; *Bacillus stearothermophilus* (calidolactis) 1 µg/ml.
16. The assessment made by the JECFA reports a study on the effects of thiamphenicol lifetime oral exposure on the spontaneous immunocomplex nephritis in NZW x OUW mouse strain. A reduction in immunocomplex deposition was observed at more than or equal to 50 mg/kg bw, indicating an immunosuppressive action. No effect was observed at 25 mg/kg bw.
17. Thiamphenicol has been widely used against human infections. The usual adult oral dose is 1500 mg daily (25 mg/kg bw in a 60 kg bw individual) for up to 15 days; dosages above 30 mg/kg bw are suggested for children.

Adequate epidemiological data did not show any increased risk for aplastic anaemia in thiamphenicol-treated patients. This might be explained by the absence of the very reactive nitro-group which is characteristic of chloramphenicol, but experimental proof of this hypothesis is lacking.

Bone marrow depression was the main side-effect observed in human patients, with a frequency of approximately 0.5%; the effect was dose-dependent and rapidly reversible following cessation of treatment. Inhibition of mitochondrial synthesis has been hypothesised as the underlying mechanism. However, a detailed appraisal of human adverse effects has not been provided; thus, a level without adverse effects in humans was not determined.

18. Thiamphenicol was evaluated by JECFA in 1996.

The JECFA considered that 1.25 mg/kg bw was the NOEL for maternal toxicity in the rabbit embryotoxicity/foetotoxicity study, and that a temporary toxicological ADI of 6 µg/kg bw should be set on that basis with a safety factor of 200, while awaiting the final report of the carcinogenicity study.

The CVMP considered the study not appropriate for ADI determination, due to the well recognised high sensitivity of the rabbit to orally administered antimicrobial chemicals.

There is no evidence that thiamphenicol is a genotoxic or carcinogenic compound; moreover, extensive human data show that, unlike chloramphenicol, thiamphenicol does not elicit any increase of aplastic anaemia, or of any other irreversible effects.

A toxicological ADI was set on the basis of the 13-week rat study. The study was of adequate quality and duration; no effects on tissues or organs were observed at the lowest dose level tested: 9.0 mg/kg bw. However, minor haematological and biochemical changes were observed down to such a dose level, which justifies a conservative safety factor of 200.

Based on the NOEL of 9 mg/kg bw, applying a safety factor of 200, a toxicological ADI of 0.045 mg/kg bw (i.e. 2.7 mg/person) was established.

This ADI of 0.045 mg/kg bw ensures an approximate safety margin of 900 as compared to the 40 mg/kg bw NOEL for post-implantation loss and maternal toxicity in the rat.

However, a lower ADI was derived from microbiological effects on human gut flora.

19. A MIC₅₀ of 0.5 µg/ml was selected as the basis for a microbiological ADI, assessed on the most sensitive species identified among those considered most relevant to human gut flora, i.e. *Fusobacterium* sp.

For the assessment of the microbiological risk, use was made of the formula that was recommended by the CVMP:

$$\text{ADI} = \frac{\frac{\text{geometric mean MIC}_{50} \times \text{CF2}}{\text{CF1}} \times (\mu\text{g/ml}) \times \text{daily faecal bolus (150 ml)}}{\frac{\text{fraction of an oral dose available for microorganisms}}{\text{weight of human (60 kg)}}}$$

Based on the above formula, the microbiological ADI was calculated as follows:

$$\text{ADI} = \frac{\frac{0.50 \times 1}{0.50} \times \frac{150}{60}}{1} = 2.5 \mu\text{g/kg bw i.e. } 150 \mu\text{g/person}$$

The following assumptions were made:

- CF1 = 1, because the most sensitive MIC₅₀ were used, and because there are no data on the induction of microbial resistance to justify the adoption of a different CF;
- CF2 = 1, because there are no data on the effects of inoculum density or pH to justify the adoption of a different CF;
- 150 g is the weight of the daily faecal bolus;
- 0.50 is a conservative estimate of the fraction of the oral dose available in the human intestinal tract assuming that more than or equal to 50 % of a dose assumed orally is excreted through the urine and that faecal excretion will account for the balance.

The microbiological ADI is in a 1:10⁵ ratio with the usual oral therapeutic dosage of thiamphenicol, thus ensuring an ample safety margin for any adverse human side-effect.

20. For the establishment of final MRLs for pigs the information summarised in the paragraphs below was taken into account.
21. Fifteen pigs were treated orally twice a day for 5 days with 10, 15 or 20 mg/kg bw thiamphenicol. Blood samples were analysed by gas chromatography with electron capture detector (limit of quantification 20 µg/l). For unchanged thiamphenicol, the samples were extracted in organic phase without enzyme hydrolysis, for the total thiamphenicol the samples were incubated with beta-glucurase before analysis. Thiamphenicol was rapidly absorbed and the area under the curve and C_{max} of unchanged thiamphenicol were linearly correlated with the dose. No accumulation of thiamphenicol or thiamphenicol glucuronide was evident in swine plasma after oral administration at doses of 10, 15 and 20 mg thiamphenicol/kg bw twice daily for five consecutive days.

In a GLP study, 16 pigs were fed twice daily with 900 mg thiamphenicol/kg feed (approximately 30 mg/kg bw) for 5 days; 3 pigs were maintained as controls. Thiamphenicol was measured in plasma following solvent extraction, using a solid-phase liquid-liquid partitioning technique and HPLC (limit of detection 0.01 µg/ml). The maximum mean level of thiamphenicol in plasma (1.28 µg/ml), was found at eight hours after the first dose administration.

Six healthy male pigs were treated with medicated water containing 2.5 ml of 10% thiamphenicol/l of water, ad libitum, for 5 days. Peak plasma concentration (mean plasma concentration at the steady state 1.01 ± 0.44 µg/ml) was reached at 36 hours after the start of treatment and the levels remained similar until the end of the treatment period (120 hours). Elimination half live (2.9 ± 0.3 hours) was determined by linear regression of the terminal phase, when treatment was stopped. Administration of thiamphenicol in water resulted in an increase in plasma levels until the peak and steady state concentration was reached at approximately 36 hours after start of administration. Elimination of thiamphenicol from plasma was rapid upon cessation of treatment.

Pharmacokinetic parameters of thiamphenicol were determined after single intravenous or intramuscular administration of 30 mg/kg bw to 5 male pigs. Three weeks later, the same animals were administered a second dose via the other route. Plasma drug concentrations were determined by HPLC (limit of quantification 20 ng/ml). Intravenous thiamphenicol kinetics were fitted to a bi-exponential equation, with a first rapid disposition phase followed by a slower disposition phase.

The thiamphenicol elimination half-life following intramuscular administration was statistically greater than following intravenous administration, probably due to the slow rate of absorption from the muscle.

Six large white male pigs (26.6 ± 4.1 kg) were administered a single dose of 30 mg/kg bw thiamphenicol intravenously. A validated HPLC analytical method with UV detection was used to determine thiamphenicol concentration in plasma. The limit of quantification of the method was 20 ng/ml. The linearity of the method was determined between 0.02 µg/ml and 15 µg/ml; precision and accuracy were below 15%. Elimination half life was short (1.2 ± 0.5 h) and there was a high rate of plasma clearance (356.4 ± 119.7 ml/min).

Three female and 3 male pigs (body weight 27 to 34 kg) were administered either 10 mg/kg bw (as solution by intravenous route) or 30 mg/kg bw (as suspension by oral route). Three weeks later the animals were administered thiamphenicol by the alternative route. Serum concentrations of thiamphenicol were determined by a validated HPLC analytical method (limit of quantification 0.05 µg/ml). The short elimination half-life and mean residence time values following intravenous administration confirm the rapid elimination of thiamphenicol in swine compared with oral administration.

Pharmacokinetics of unchanged thiamphenicol and thiamphenicol glucuronate were determined in 4 swine administered thiamphenicol orally at 30 mg/kg bw in the feed and thiamphenicol intravenously at 10 mg/kg bw as glycinate, following a cross-over design. Both free and total thiamphenicol were assayed in plasma and urine samples, according to GLP requirements, using a validated HPLC-UV method (limit of quantification 21 µg/l for plasma and 210 µg/l for urine). Concentrations of glucuronate thiamphenicol were determined by subtracting the quantity of free thiamphenicol from that of total thiamphenicol. In urine, highest concentrations of total thiamphenicol occurred 4 hours after oral administration and ranged between 610 and 723 mg/l. After intravenous administration, maximum urine concentrations also occurred after 4 hours with a range of 363 to 1136 mg/l. The area under the curve after oral administration for total thiamphenicol is about 4 times that of free thiamphenicol. Following intravenous administration, this ratio is only 2 times, suggesting that glucuronidation after oral administration is much higher than after intravenous administration.

For total thiamphenicol, the average elimination ratio, half life and distribution volume are similar in both routes of administration. Elimination parameters of free thiamphenicol are similar for the 2 routes of administration.

In a GLP study, thiamphenicol was administered to 2 groups of 4 pigs each. One group was treated orally at a dose rate of 30 mg thiamphenicol/kg bw, once daily for 3 consecutive days. The other group was administered thiamphenicol intramuscularly at a dose rate of 30 mg/kg bw once daily for 3 consecutive days. After a washout period of 11 days animals in the first group were administered thiamphenicol intramuscularly and those in the other group received thiamphenicol in the feed. After intramuscular administration, blood samples were taken at 0, 0.25, 0.5, 1, 2, 6 and 12 hours after the first administration, 0, 1 and 12 hours after the second administration and 0, 1, 12, 24, 36 and 48 hours after the third administration. Following oral administration, blood samples were taken at 0, 0.5, 1.5, 3, 5, 7 and 12 hours after the first administration, 0, 1.5 and 12 hours after the second administration and 0, 1.5, 12, 24, 36 and 48 hours after the third administration. Determination of thiamphenicol in plasma was carried out using an HPLC/MS/MS analytical method fully validated in the range 0.20 to 20.00 µg/ml; the limit of quantification and limit of detection were 0.20 and 0.05 µg/ml, respectively. The results show a rapid absorption following both routes of administration though intramuscular administration leads to a higher plasma concentration and a higher bioavailability following intramuscular administration. The relative bioavailability of the oral route to the intramuscular route was approximately 48%. The elimination half lives were comparable for the two routes of administration. The absence of difference in plasma concentrations achieved after the first, second or third day demonstrated absence of accumulation for each of the routes of administration tested.

22. In a GLP study 32 pigs were administered daily 30 mg thiamphenicol/kg bw intramuscularly for 5 days. Groups of 2 males and 2 females were slaughtered at either 8 hours, 1, 4, 8, 15, 21 or 28 days after treatment. Administration was made into the left side of the neck on days 1 to 4 and into the right side of the neck on day 5. Tissue samples were taken for determination of residues of free thiamphenicol by HPLC method (the limit of detection and limit of quantification were 5 µg/kg and 21 µg/kg, respectively, for all matrices). The kidney showed the highest concentration of thiamphenicol 24 hours after the last treatment (6 675 µg/kg), 1 648 µg/kg at 8 hours, 54.99 µg/kg at 4 days and 24.18 µg/kg after 8 days. In muscle the mean concentration of thiamphenicol was 389,5 µg/kg at 24 hours after the last administration and decreased rapidly to an estimated mean value of 10.75 µg/kg after 4 days. Traces of thiamphenicol were detected up to 21 days. In liver 24 hours after the last treatment, the mean thiamphenicol residue value was 111 µg/kg and depleted rapidly, 4 days after the last treatment all samples showed values below the limit of quantification. The mean concentration of thiamphenicol in skin + fat was 32,4 µg/kg 4 days after the last treatment and 16.91 µg/kg after 8 days (below the limit of quantification in 3 samples out of 4). In the injection site after 8 days of treatment the mean residue concentrations were 34.64 µg/kg and 13.81 µg/kg at 15 days after the last treatment. Traces of thiamphenicol were detected up to 21 days after the last treatment.

In a GLP study, 9 male pigs were administered daily for 5 or 6 days at 50 mg/kg bw of thiamphenicol by intramuscular route. Groups of 3 animals were slaughtered at either 2 hours, 8 hours or 4 days after the last treatment. Tissue samples were assayed for residues of thiamphenicol according to a microbiological method and a HPLC method. The limit of detection and limit of quantification of the HPLC method were, respectively, 15 and 25 µg/kg for all tissues. Results of determination of residues of free thiamphenicol and total thiamphenicol by the HPLC method showed that 4 days after the end of treatment free thiamphenicol was not detectable in kidney, liver and muscle and total thiamphenicol was not detectable in liver and muscle. Eight hours after the last administration high concentrations of thiamphenicol glucuronate were found in tissues, representing more than 30% of the total thiamphenicol residues in kidney, liver and skin+fat, and near 5% in muscle. Four days after the end of treatment the concentration in kidney of total thiamphenicol was 25.0 µg/kg and the concentration of free thiamphenicol was below the limit of quantification (25.0 µg/kg), in skin+fat the concentration of total thiamphenicol was 54.0 µg/kg and the concentration of free thiamphenicol was 47.2 µg/kg. As 4 days after the end of thiamphenicol administration tissue residues of total thiamphenicol were near or below the limit of detection (apart from those for skin+fat), at 8 hours free thiamphenicol was only a portion of total thiamphenicol for kidney, liver and skin+fat and no results were provided between 8 hours and 4 days, therefore no conclusion could be drawn from this study on the ratio between free thiamphenicol and total thiamphenicol in pigs.

In a GLP study 2 female pigs were intramuscularly administered 0.2 ml of an aqueous solution containing thiamphenicol (equivalent to 50 mg thiamphenicol/kg bw) per day for 5 days, in a study following the GLP principles. The animals were sacrificed at 4 and 8 hours after the last administration, respectively. Free thiamphenicol levels were determined simultaneously in the tissue samples using validated HPLC/UV and microbiological (diffusion assay, using *Bacillus stearothermophilus*) method. Both methods were validated in the range 1 000 to 6 000 µg/kg with a limit of quantification of 1 000 µg/kg for all tissues. The injection site showed the highest concentrations of free thiamphenicol, 1 323 215 and 1 175 000 µg/kg by HPLC and microbiological method respectively in one pig sacrificed 4 hours after the last administration and 149 635 and 138 100 µg/kg in the pig sacrificed at 8 hours. High tissue concentrations were obtained by HPLC and microbiological method in kidneys: 35 920 and 33 995 µg/kg, respectively, at 4 hours and 14 150 and 15 535 µg/kg at 8 hours. In muscle the concentrations resulted in 6 351 and 5 805 µg/kg respectively at 4 hours and 2 738 and 2 678 at 8 hours after the last administration. In liver the values by HPLC and microbiological method were 4 700 and 4 910 µg/kg at 4 hours, 2 510 and 2 110 µg/kg at 8 hours. The lowest residues of thiamphenicol were obtained in skin+fat samples, 2 095 and 2 040 µg/kg at 4 hours by HPLC and

microbiological method, 548 µg/kg by HPLC at 8 hours (below the sensitivity limit of the microbiological method, 1000 µg/kg). The correlation between the results of the two assay methods was approximately 1.

In a GLP study, 21 pigs were assigned to five groups of four animals (2 male and 2 female) each and 1 control female animal. The 5 treatment groups received thiamphenicol by the intramuscular route in the neck once a day for 5 consecutive days at a dose of 0.2 ml/kg bw/day, equivalent to 50 mg thiamphenicol/kg bw/day. Animals in groups 1 to 5 were sacrificed at 8, 12, 24, 48 or 96 hours respectively after the last administration. The determination of thiamphenicol in muscle, liver, kidney and skin with adhering fat and muscle injection site was carried out simultaneously, on the same samples, using validated chemical and microbiological methods. The chemical determination of free thiamphenicol was performed by HPLC connected to a UV or MS/MS detector depending on the range concentration. The HPLC/UV method was validated in the range 1 000 to 6 000 µg/kg. One HPLC/MS/MS method was validated in the range 25 to 100 µg/kg for all tissues and the other HPLC/MS/MS method in the range 100 to 400 µg/kg (muscle, skin+fat) and 100 to 600 µg/kg (liver, kidney). The microbiological method was validated in the range 1 000 to 6 000 µg/kg for all tissues (diffusion assay, using *Bacillus stearothermophilus*) and between 100 and 600 µg/kg for liver, 100 and 400 µg/kg for muscle and skin+fat and between 200 and 600 µg/kg for kidney (turbidimetric assay, using *Haemophilus influenzae*). Comparable results in all edible tissues were obtained by HPLC and microbiological methods. The HPLC values of free thiamphenicol in different tissues were; kidney 34 578 µg/kg at 8 hours, 15 528 µg/kg at 12 hours, 3 778 µg/kg at 24 hours, 594 µg/kg at 48 hours and 329 µg/kg at 96 hours after the last treatment; in muscle 4 399 µg/kg at 8 hours and 2 389 µg/kg at 12 hours, 274 µg/kg at 24 hours, 65 µg/kg at 48 hours and 35 µg/kg at 96 hours. The injection site showed high concentrations of thiamphenicol, 1 554 189 and 1139 128 µg/kg at 8 and 12 hours, 5 581 µg/kg at 24 hours, 71 µg/kg at 48 hours and 39 µg/kg at 96 hours. The lowest values were found in liver (1816 µg/kg, 902 µg/kg, 130 µg/kg, 89 µg/kg and 59 µg/kg as mean residue respectively from 8 to 96 hours after the last treatment) and in skin+fat (1034, 531, 101, 113 and 82 µg/kg respectively from 8 to 96 hours). For all tissues the individual and mean results obtained by microbiological method were similar to the values obtained by HPLC at all sampling times until 48 hours after the last treatment. Since the ratio is approximately 1 (ranging from 0.84 to 1.15), this suggests that glucuronated thiamphenicol, or any other metabolite of thiamphenicol present in edible pig tissues, is not microbiologically active *in vitro*.

Twelve pigs were administered thiamphenicol orally daily for 5 days at 40 mg/kg bw, divided into two daily administrations; 2 animals were slaughtered at 5, 8, 10, 11, 12 and 15 days after the last administration. Tissue samples were taken for determination of residues of free thiamphenicol according to a validated HPLC method (limit of quantification 20 µg/kg). The maximum level of residues were always observed at 5 and 8 days after treatment; the most persistent residues were in liver and kidney. Free thiamphenicol mean levels in muscle were 32 µg/kg, 108,9 µg/kg and below the limit of quantification from 5 to 15 days after the last treatment; in skin+fat the results were 32,2 µg/kg and below the limit of quantification respectively from 5 to 15 days after the last treatment; in liver 97,75 µg/kg, 102,15 µg/kg and 23 µg/kg and below the limit of quantification respectively from 5 to 15 days after the last treatment; in kidney 641 µg/kg, 964 µg/kg 261,5 µg/kg, 41,9 µg/kg and below the limit of quantification respectively from 5 to 15 days after the last treatment.

In a GLP study, 20 pigs, 2 month-old, 35 to 42 kg bw were allocated in 4 groups of 5 animals and administered thiamphenicol at 30 mg/kg bw/ day (divided into 2 daily administrations) for 5 days in the feed. The animals were sacrificed at 5, 10, 16 or 18 days after treatment. Tissues were assayed for residues of free thiamphenicol, using a validated HPLC-UV method (limit of detection 5 µg/kg and limit of quantification 21 µg/kg). Residues of free thiamphenicol were not detected at any time in muscle, except in 2 animals at the fifth and tenth day after the last administration (534,58 and 127,68 µg/kg, respectively), while subsequently the values decreased to 83,52 µg/kg and 39,14 µg/kg after 16 and 18 days. In liver residues were 56,28 µg/kg 5 days

after treatment and 38,45 µg/kg 10 days after treatment, while they fall to 22,45 and 27,35 µg/kg at day 16 and 18, respectively. Skin showed elevated residual concentrations of free thiamphenicol with a mean value of 94,60 µg/kg even at the final slaughter time, fat showed limited concentrations at all time periods, with mean value of 7.10, 11.26, 9.09 and 5.59 µg/kg, at 5, 10, 16 and 18 days after the last treatment respectively.

23. Twenty male and twenty female pigs were treated with thiamphenicol, by intramuscular injection, at a dose rate of 50 mg/kg/day. The drug was administered, alternatively, to both sides of the neck. Samples of liver, kidney, skin+fat, muscle and both injection sites were obtained at 1, 2, 4, and 7-day withdrawal periods (10 animals per sampling time). The tissue samples collected were analyzed before and after deconjugation of glucuronconjugated thiamphenicol with β-glucuronidase. The analytical method consists of an HPLC/MS/MS. The limit of quantification of the analytical technique was 20 µg/kg for all the tissues. The study was GLP compliant. The higher free thiamphenicol tissue concentrations were found in the injection sites and decline from more than 5000 µg/kg in the left injection site at 1 day withdrawal to 521 µg/kg in the right injection site at 7 days withdrawal. The tissue with less free thiamphenicol residue was the uninjected muscle with 136 µg/kg at 1-day withdrawal to less than the limit of quantification at 2 days withdrawal time. The ratio of free thiamphenicol concentrations to total thiamphenicol concentration in the muscle samples was close to 1, indicating that in this tissue no conjugated thiamphenicol residues were found. The ratios of free thiamphenicol concentrations to total thiamphenicol concentration were between 0.63 and 1.00 in liver, between 0.44 and 1.00 in kidney and between 0.52 and 0.62 in fat+skin, the kidney being the tissue with higher concentrations until 7-day withdrawal time.

In the same experiment, the animals to be sacrificed at 7-day withdrawal time were housed in individual metabolic cages to obtain samples of faeces and urine during and after drug administration. For the urine and faeces samples a complete validation of HPLC/MS/MS method is presented with a limit of quantification of 100 µg/kg. The faecal and urinary depletion of free thiamphenicol and conjugated thiamphenicol was very fast. While in faeces the ratio free thiamphenicol to total thiamphenicol was close to 1 in all the samples obtained after last drug administration, in the urine samples this ratio increases from 0.350 at 1 day withdrawal to 1 at 4 days withdrawal.

24. HPLC/MS/MS routine analytical methods for determining thiamphenicol residues in pig tissues are available. The methods are presented in ISO 78/2 format, and validated according to Volume 8 of the Rules Governing Medicinal Products in the European Union. The limits of quantification for all tissues are less than 25 µg/kg. The specificity of the analytical methods in respect to chloramphenicol and florfenicol is demonstrated.
25. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) previously established an ADI of 2.5 µg/kg and temporary MRLs in muscle, liver, kidney and fat for pigs. The temporary MRLs were 0.05 mg/kg for muscle, liver, kidney and fat (pigs) expressed as the sum of thiamphenicol and its conjugates, measured as thiamphenicol. However, these were not extended in 1999 because the information requested by JECFA was not provided.
26. For the extension to include all food producing species in Annex I the information summarised in the paragraphs below was taken into account.
27. A residue depletion study was performed in sixteen beef calves administered orally 50 mg/kg bw of thiamphenicol, subdivided in two daily administrations for 4 days. Thiamphenicol residues were analysed by HPLC (limit of detection 20 µg/kg). Liver residues ranged from 65 to 77 µg/kg 4 days after the end of treatment, 20 to 75 µg/kg after 6 days, while only one out of 4 samples showed residues equal to the limit of detection after 8 days. Kidney residues ranged from 50 to 115 µg/kg after 4 days; one out of 4 samples showed residue concentrations of 120 and 20 µg/kg after 6 and 8 days, respectively. No residues were observed in muscle, besides a single sample with residue concentrations of 90 µg/kg after 6 days. All samples examined at day 10 after treatment showed no detectable residues.

No examination was performed as regards residues in body fat.

28. Four each high-yield cows and low-yield cows were treated intramuscularly with a total daily thiamphenicol dose of 30 mg/kg bw, divided into two 15 mg/kg bw injections for 5 days. Residues more than or equal to 800 µg/kg were detected in the milk one day after stopping administration. After 2 days, the residues in milk of 6 out of 8 cows were below the quantification limit of the gas-liquid chromatography-electron capture detector method utilised (20 µg/kg), whereas the residues in the milk of 2 out of 8 cows were 124.5 and 34.1 µg/kg, respectively. No detectable residues were present 72 hours after the cessation of treatment.
29. A milk residue study by intramammary route was conducted to compare two different formulations with 5% and 10% thiamphenicol glycinate acetylcysteinate. Six Friesian dairy cows underwent two treatment cycles, during which 500 mg of thiamphenicol in each quarter were administered 3 times at 12-hour intervals. A 12-day interval separated the treatment cycles with the two formulations.

In each treatment cycle, milk samples were collected at the milking immediately before the first administration and for the following six days.

With the 5% formulation, mean milk residues were 85 µg/kg (0.034 to 0.172) at the second milking after the cessation of treatment, 35 µg/kg in 2 out of 6 cows at the 3rd milking (4 out of 6 cows below the 20 µg/kg limit of quantification) and below the limit of quantification for all cows at the fourth milking.

With the 10% formulation, mean milk residues were 264 µg/kg (36-600) at the second milking after the cessation of treatment, 28 to 93 µg/kg in 4 out of 6 cows (2 out of 6 below the limit of quantification) at the third milking, 21 to 54 µg/kg in 2 out of 6 cows (4 out of 6 below limit of quantification) at the fourth milking, 26 µg/kg in a single animal at the fifth milking; all animals showed residues below the limit of quantification at the sixth milking after the cessation of treatment.

The study was not a standard residue depletion study; thus it has a limited value in assessing the residue depletion curve in milk after intramammary administration.

30. Since no tissue depletion residue studies were performed in cattle following intramuscular administration, there is no information on the depletion of thiamphenicol residues at the injection site.
31. Total radioactive residues were investigated in 48 broiler chickens treated orally with 50 mg/kg bw ¹⁴C-thiamphenicol subdivided into two daily doses for five and a half days.

Liver concentrations averaged 7.80, 3.55, 1.80 and 1.16 mg equivalents/kg after 6 hours, 1, 3 and 5 days following the last treatment, respectively. Mean kidney concentrations at the same sampling times were 4.90, 1.70, 0.91 and 0.82 mg equivalents/kg. In muscle, radioactivity fell from 1.12 mg equivalents/kg at 6 hours to 0.34, 0.20 and 0.16 mg equivalents/kg at 24, 96 and 72 hours, respectively. Abdominal fat concentrations averaged 0.50, 0.21, 0.14 and 0.12 mg equivalents/kg at 6 hours, 1, 3 and 4 days; at the corresponding sampling times skin+fat concentrations were 1.35, 0.52, 0.54 and 0.38 mg equivalents/kg, respectively.

The tissue residue depletion profile of thiamphenicol was investigated in 96 broiler chickens following treatment with a dose of 840 mg/l in drinking water for 5 days, equal to an average intake of 134 mg/kg bw/day. Animals were slaughtered at 2, 4, 6, 8 hours, 1, 2, 4 and 17 days after the last treatment day.

Mean liver residues were (range) 310.2 (62.9 to 651.7), 257.4 (46.6 to 452.1) and 146.6 (58.1 to 302.6) µg/kg after 1, 2 and 4 days, respectively. After a 17-day withdrawal, residues ranged from 7 to 21 µg/kg in liver (2 out of 6 samples below limit of detection). Mean kidney residues were 382.6 (46.5 to 741.2), 64.4 (28.8 to 132.4), and 23.9 (1 out of 6 sample below limit of detection) µg/kg after 1, 2 and 4 days, respectively; no detectable residues were present after 17 days. Mean breast muscle residues were 852.4 (112.2 to 3500.9), 285.3 (139.5 to 398.7) and 78.6 (29.3 to 156.3) µg/kg after 1, 2 and 4 days, respectively. After 17 days, residues ranged from 4.6 to 57.8 µg/kg in breast muscle (1 out of 6 samples below limit of detection). Skin

with adhering fat showed high residue concentrations at all sampling times, namely (average values): 20100 µg/kg at 2 hours after the cessation of treatment, 19500 µg/kg at 4 hours, 5900 µg/kg at 6 hours, 18600 µg/kg at 8 hours, 28000 µg/kg after 1 day, 9300 µg/kg after 2 days, 4200 µg/kg after 4 days and 5,100 µg/kg after 17 days. Average thiamphenicol concentrations in abdominal fat were (range): 4900 (1000 to 14900) µg/kg at 2 hours after the cessation of treatment, 4000 (800 to 9300) µg/kg at 4 hours, 5200 (1000 to 7900) µg/kg at 6 hours, 1100 (500 to 1700) µg/kg at 8 hours, 3800 (600 to 8400) µg/kg after 1 day, 960 (770 to 1320) µg/kg after 2 days, 200 (80 to 490) µg/kg after 4 days, 150 (40 to 490) µg/kg after 17 days.

All residue concentrations above 1000 µg/kg were estimated, because they are above the concentrations for which the HPLC method is validated. Therefore, no firm conclusions could be derived about most quantitative residue values in skin+plus fat and abdominal fat, especially at the earlier sampling time points.

32. Fifteen laying hens were exposed through the diet to thiamphenicol at a dose level of 400 mg/kg feed, equal to 30 mg/kg bw, for 5 days. The whole eggs (yolk plus albumen) were examined for the presence of thiamphenicol residues from 1 up to 14 days following cessation of the treatment.

Residues of unchanged thiamphenicol ranged from 72 to 190 µg/kg and 20 to 43 µg/kg (with 50% of hens showing no detectable residues in their eggs), respectively, 4 and 7 days after the end of treatment. A single hen, out of 13, showed detectable residues (23 µg/kg) 8 days after the end of treatment. Residues below the limit of quantification (less than 20 µg/kg) residues were observed after 9 days. The study shows some potential for thiamphenicol accumulation and persistence in the eggs; thus, no MRLs for eggs are proposed.

33. Kinetic and distribution of thiamphenicol in sheep were studied in two experiments. In the first study, 18 sheep were treated by intravenous route (9 animals) and by intramuscular route (9 animals) with thiamphenicol at 20 mg/kg bw. Blood samples were collected until 10.5 hours after drug administration and analysed by HPLC (limit of detection: 100 µg/l) for the determination of thiamphenicol. After intravenous injection of 20 mg/kg, $t_{1/2\alpha}$ was 0.18 hours and $t_{1/2\beta}$ was 1.53 hours. The apparent volume of distribution, steady state volume of distribution and distribution volume during the elimination phase are about 0.36, 0.80 and 1.09 l/kg respectively. The median values of K_{12} , K_{21} and K_{el} were 1.59, 1.26 and 1.26 h⁻¹ respectively. Following intramuscular administration, peak plasma concentration is reached within 10 to 20 minutes, with bioavailability of 87.5%. In the second study 10 sheep were treated by oral route and by intravenous route with 60 mg thiamphenicol/kg bw. Blood samples were collected until 24 hours after drug administration and analysed for the level of thiamphenicol by HPLC (limit of detection: 0.1 µg/ml). After intravenous and oral administration of 60 mg/kg, the drug is detected in plasma 10 minutes after treatment, with maximum concentrations of about 2.5 µg/ml after 6 hours post-treatment. These very low concentrations were maintained for 24 hours. The AUC oral was 29.98 µg·h/ml (only 30% of oral dose is systemically available).

Twelve sheep were treated by intramuscular route with 20 mg/kg bw of thiamphenicol every 8 hours for 4 times. Blood samples were collected until 8 hours after the third drug injection. Samples of biological fluids (blood, bile, pericardial, peritoneal, synovial and cerebrospinal fluids) were collected at 2, 6, 12, 24, 48 and 72 hours after last treatment and analysed for the determination of thiamphenicol by HPLC (limit of detection: 10 µg/l). Thiamphenicol is rapidly absorbed from injection sites yielding peak plasma concentrations of about 20 µg/ml within 30 minutes. Following, plasma concentrations declined with an elimination half life of 1.51 ± 0.51 hours and a mean residence time of 2.05 ± 0.51 hours. In biological fluids, the mean concentrations of the antibiotic became undetectable after 24 hours (with the exception of the cerebrospinal fluid) with mean values comprised in the range from 9.75 to 31.25 µg/ml after 2 hours and from 0.5 to 1.25 µg/ml at 24 hours. These values are higher than the corresponding plasma concentrations. In the cerebrospinal fluid the substance is detected only at 2 and 6 hours.

34. Sixteen sheep divided into four groups were treated once a day for 5 consecutive days by intramuscular administration with 30 mg/kg bw/day of thiamphenicol (0.12 ml/kg/day of a commercial product). Samples of kidneys, liver, visceral fat muscle and injection site were collected at 4, 8, 12 and 16 days after the end of treatment and analysed by HPLC (limit of

quantification: 21 µg/kg). Thiamphenicol was detected in 3 kidney samples out of 4 collected after 4 day withdrawal period. The mean thiamphenicol concentration was 40 µg/kg (individual values ranging from 22 to 117 µg/kg). Thiamphenicol was no longer detected in the kidney at the subsequent withdrawal periods. Liver samples did not show detectable levels of thiamphenicol. The mean concentration of residues in the abdominal fat was 342 µg/kg after 4 day withdrawal period. Only thiamphenicol traces were found in 2 fat samples collected 8 and 12 days after the last treatment. After 4 days concentration of 50 µg/kg of thiamphenicol were found in the neck muscle, where the test compound was injected. Quantifiable residues were detected up to 16 days after the end of treatment. In the muscle, thiamphenicol was already not quantifiable after a 4 days withdrawal period.

35. Fish were treated by oral route with two different doses of thiamphenicol (15 and 30 mg/kg bw/day) in single and repeated treatments (5 days). Water temperature: 15±2°C. Blood samples (6 animals at each sampling time) were collected up to 72 hours after dosing in the single-dose experiment and over 14 days after the end of treatments in the repeated-dose study and analysed for the presence of thiamphenicol by HPLC (limit of quantification: 50 µg/ml). The absorption of thiamphenicol from medicated feed was slow and limited in comparison with the absorption with the force fed administration. Thiamphenicol concentrations in blood declined quickly and were under the limit of quantification of 50 µg/ml 7 days after the end of treatment.

Some pharmacokinetic studies were performed in young yellowtail fish. Thiamphenicol was administered as a single dose mixed in feed at the dose of 100 mg/kg bw. Blood samples were collected 3, 6, 12, 24 and 48 hours after administration from 7 fish per timepoint. The results obtained by colorimetric method indicated a peak-concentration 3 to 6 hours after administration (C_{max} : 9.4 to 12.1 µg/ml) and disappearance from the blood in 48 hours. In fish, high levels of thiamphenicol were measured in bile 24 hours after oral administration.

36. Thiamphenicol was administered mixed with feed to sea bass (*Dicentrarchus labrax*) at the dose of 40 mg/kg bw/day for 5 days. Samples of muscle, liver, skin and vertebrae from 10 fish per timepoint were collected on day 2 and 4 of treatment and on days 1, 2, 3, 5, 7 and 10 after the end of treatment and analysed by HPLC (limit of quantification: 20 µg/kg and 50 µg/kg for skin). Three days after the end of treatment the levels of thiamphenicol ranged between 28 and 30 µg/kg (only 3 samples out of 10 were positive) in muscle and were below the limit of quantification of the HPLC method (50 µg/kg) in skin.

Residue depletion of thiamphenicol was also studied in sea-bream (*Sparus aurata*) administered with the feed at the dose dose of 40 mg/kg bw/day for 5 days. Samples of muscle, liver, skin and vertebrae from 10 fish per timepoint were collected on day 2 and 4 of treatment and on days 1, 2, 3 and 5 after the end of treatment and analysed by HPLC (limit of quantification: 20 µg/kg for muscle and 50 µg/kg for skin). Three days after the end of treatment the levels of thiamphenicol were 30 µg/kg in muscle (only three samples out of ten were positive) and were below the limit of quantification of the HPLC method in skin.

Thiamphenicol was administered mixed with feed to young yellowtails at the dose of 45 mg/kg bw/day and 90 mg/kg bw/day for 14 days. Muscle, liver kidney and skin with fat were sampled on the tenth day of administration and 0, 3, 7, 10, 14, 21 and 28 days after the end of treatment. The highest residual levels were found in liver, followed by kidney, skin and muscle and fell below the limit of quantification (20 µg/kg by gas-chromatographic method) in all tissues examined 3 days after the end of treatment.

37. While the available data did not allow a detailed quantitative assessment of the ratio of marker residue to total residue, on the basis of the results of pharmacokinetic and residue studies, thiamphenicol does not undergo major phase I biotransformation processes in the species bovine, porcine and chickens as well as in humans. Unchanged thiamphenicol was considered as the marker residue for bovine, chicken and fish tissue.
38. Two analytical methods have been validated for thiamphenicol in bovine and poultry tissues and bovine milk:

- a gas-liquid chromatography method with electron capture detection (GLC-ECD) for the determination of thiamphenicol in cow's milk: the method uses chloramphenicol as the internal standard; the peak height ratios of thiamphenicol/chloramphenicol of the standard concentrations of the calibration curve are used for the quantification; the limit of quantification is 20 µg/kg;
- an HPLC method for the determination of thiamphenicol in bovine and poultry tissues: the limit of quantification for all relevant bovine and poultry tissues is 20 µg/kg; the limit of detection for bovine tissues is 2.5 µg/kg for muscle, 2.6 µg/kg for liver and fat, and 5.1 µg/kg for kidney. As regards chicken, the limit of detection is 2.6 µg/kg for kidney and skin, 2.9 µg/kg for muscle, 5.1 µg/kg for fat, and 5.8 µg/kg for liver.

Both methods were presented in ISO 78/2 format.

39. The available pharmacokinetic and residues depletion data do not indicate any significant variability between pigs, cattle and chicken, therefore, it was considered that other animal species were unlikely to show any significant differences in these parameters. The existing tissue MRLs for bovine, and chicken species, and the final recommended MRLs for porcine species are identical and so it was considered appropriate to recommend the extension of the MRLs so that that these MRL values would apply to food producing species. The MRL for bovine milk is recommended to be extrapolated to all food producing species.

CONCLUSIONS AND RECOMMENDATION

Having considered that:

- a microbiological ADI of 2.5 µg/kg bw (150 µg/person) was previously established for thiamphenicol based on microbiological effects on human gut flora,
- thiamphenicol was retained as the marker residue for all food producing species,
- the same MRLs had previously been established in bovine and chicken,
- provisional MRLs for porcine can now be confirmed as final,
- the provisional MRLs previously set for ovine and fin fish previously had the same values,
- extrapolation of these MRLs to all food species is now possible,
- a validated analytical method for monitoring residues of bovine, porcine and chicken tissues and bovine milk, is available and that the method is also considered to be applicable to all food producing species;

The Committee for Medicinal Products for Veterinary Use recommends the inclusion of thiamphenicol into Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Thiamphenicol	Thiamphenicol	All food-producing species	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg	Muscle* Fat** Liver Kidney Milk	Not for use in animals from which eggs are produced for human consumption. MRLs for fat, liver and kidney do not apply to fin fish

* For fin fish this MRL relates to "muscle and skin in natural proportions".

** For porcine and poultry species this MRL relates to "skin and fat in natural proportions"

It was estimated that extending the MRLs to all food producing species, as proposed above would result in a consumer intake not exceeding 71% of the ADI.