



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

THIAMPHENICOL

SUMMARY REPORT (1)

1. Thiamphenicol is a broad-spectrum antibiotic closely related to chloramphenicol.

Following the examination of the dossier submitted by the applicant and discussion within the Working Group on the Safety of Residues of the Committee for Veterinary Medicinal Products several topics have been addressed as highly relevant for the establishment of maximum residue limits (MRLs) for thiamphenicol, namely :

- a) Comparison between thiamphenicol and chloramphenicol metabolism;
 - b) Occurrence of aplastic anaemia following thiamphenicol treatment;
 - c) Prenatal toxicity;
 - d) Effects on human gut flora;
 - e) Oral bioavailability in humans;
 - f) Residues in the target species.
- a) Thiamphenicol chemical structure differs from that of chloramphenicol in having a sulpho-group instead of a nitro-group; consequently the two compounds have different metabolic pathways. In fact thiamphenicol, unlike chloramphenicol, is not an optimal substrate for the hepatic microsomal enzyme glucuronyl transferase and therefore more than 95% of the administered dose is excreted unchanged in laboratory animals; when tested *in vitro* on pig hepatocytes, approximately 30% of thiamphenicol undergoes glucuronidation. Only 15-20% of chloramphenicol is excreted as parent compound. Moreover, some arylamine is found in the urine of chloramphenicol-treated animals, deriving from the reduction of the nitro-group. Of course, no arylamine is present after treatment with thiamphenicol.
 - b) A rare but potentially fatal aplastic anaemia associated with chloramphenicol treatment may occur in humans. The disease may have an idiosyncratic basis and the risk of occurrence does not show a clear dose-response relationship.

With regard to thiamphenicol the available epidemiological data indicate that thiamphenicol-treated patients do not show any increased risk for aplastic anaemia.

- c) Adverse effects were not observed in prenatal (segment II) toxicity studies in the rat. In the rabbit maternal toxicity and reduced foetal weight were observed at the highest dose level (40 mg/kg bw). At the lowest dose level (5 mg/kg bw) lower foetal weight was still observed with borderline significance. No effects were detected in a subsequent pilot segment II-study in the rabbit where 5 mg/kg bw was the highest dose level (6 litters per dose level).

It is widely recognised that prenatal toxicity studies with antibiotics in the rabbit are both very difficult to perform and of little predictive value, as a single administration can lead to a marked alteration in the gut flora and fauna. This in turn will elicit evident maternal toxicity and poor digestive processes and endogenous production of vitamins due to the high sensitivity to antimicrobials of rabbit intestine content.

The 5 mg/kg bw dose level can be assumed as marginal NOEL: however, the maternal and foetal toxicity of thiamphenicol in the rabbit are most likely induced by its antimicrobial activity. The evaluation of minimum inhibitory concentration (MIC) data would thus appear as the most relevant parameter to assess the ADI and subsequently to derive MRLs.

- d) With regard to MIC assessment, it must be borne in mind that at the time the studies were carried out, little information was available to recommend the selection of bacteria strains representative of the human gut flora.

If *Bacteroides* sp. and *Peptostreptococcus* sp. are assumed to be representative of Gram-negative and Gram-positive bacteria, respectively, an assessment can be tentatively performed according to the following parameters (36th JECFA report, 1990) :

- d.1) *Modal MIC value* = 2 µg/ml (Sutter et al., 1976) for both species considered. This modal MIC should then be divided by a factor 10 in order to cover the range of MICs of more sensitive bacteria.
- d.2) *The pH of the medium* has no effect on MIC values for *Bacteroides*. No data are available for *Peptostreptococcus*.
- d.3) *Inoculum size* may affect MIC values. A 2-4 fold increase in MIC has been observed upon increasing the number of *Bacteroides* cells/ml from 10^5 to 10^7 . No data are available for *Peptostreptococcus*. Thus a factor 8 may be proposed to extrapolate to the bacterial density in human gut, i.e. 10^{11} .

However, the approach summarised above is still to be validated and it was agreed that it should so far be considered as a proposal for discussion.

- e) According to Kunin et al. (1960) 30% of the total thiamphenicol dose is excreted in urine during 48 hours following oral administration to humans, as measured in six healthy individuals.
- f) Studies on residues in the target species were performed on dairy and beef cattle and on broilers. No data are available with regard to thiamphenicol residues in eggs. Therefore it is not possible to set an MRL for this food commodity,
- f.1) Studies in dairy cattle were performed by means of gas chromatography (detection limit = 0.05 µg/ml). The results showed that no measurable residues are found in milk from 26 hours after the last parenteral treatment.
- f.2) Studies in beef cattle were performed by means of HPLC (detection limit = 20 µg/kg). Residues close to the detection limit are present in liver and kidneys eight days after treatment, while no measurable residues are found after ten days.
- f.3) In broilers treated *per os* no measurable residues are detected by HPLC in any tissue three days after the last treatment.
2. The Committee for Veterinary Medicinal Products agreed that it would be inappropriate to estimate an ADI for thiamphenicol due to the incomplete basis provided for it by either the toxicological data or the *in vitro* microbiological data.
3. However, no evidence had shown that thiamphenicol residues could constitute a major toxicological risk. As 40 µg/kg appeared to be the lowest level consistent with practical analytical methods available for residue analysis (e.g. HPLC), the CVMP set a provisional MRL for bovine and poultry meat at this level.
4. Additional information is requested before 31 December 1994 regarding the following :
- Prenatal toxicity in the rabbit with a more precise definition of a NOEL;
 - More detailed information about the effects on Gram-positive human gut flora;
 - More data on pharmacokinetics with special emphasis on the possible transfer of thiamphenicol in eggs and milk.