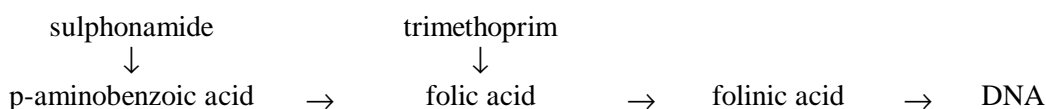


## COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

### TRIMETHOPRIM

#### SUMMARY REPORT (1)

1. Trimethoprim is active against a wide range of microorganisms including *E. coli* and some *Klebsiella*, *Proteus* and *Staphylococcus* species. It is normally used in combination with a sulphonamide and prevents the conversion of folic acid into folinic acid in the bacterial or protozoal cell, by inhibiting the enzyme dihydrofolate reductase and consequently affecting DNA synthesis :



2. Trimethoprim is of low acute mammalian toxicity with acute oral LD50 values in the range 1500 (rat) - 5400 (mouse, female) mg/kg bw. There is no evidence for the potentiation of acute toxicity when trimethoprim is administered in combination with a sulphonamide.

In sub-acute and sub-chronic studies in rats, dogs and primates, the main toxic effects were on the haematopoietic system. Effects were also observed on the adrenal, pituitary and thyroid gland, although the effects on the thyroid were probably associated with the sulphonamide administered concurrently. There was some evidence from a primate study that trimethoprim might potentiate the effect of the sulphonamides in inhibiting thyroidal iodine uptake. NOELs included 3.3 mg/kg bw per day (based on changes in some organ weights) in a 13-week study in Sprague-Dawley rats and 2.5 mg/kg bw per day (based on changes in white blood cell counts and serum cholesterol levels) in a 90-day study in Beagle dogs.

The chemical structure of trimethoprim (an aromatic amine) and its mode of action (affecting bacterial DNA synthesis) suggest that it would give positive results in some mutagenicity assays. It was mutagenic in several Ames tests using *S. typhimurium* TA88 and TA1538 and the incidence of micronuclei was significantly increased in the bone marrow of humans administered trimethoprim. However, trimethoprim was not mutagenic in a rat dominant lethal assay and no chromosome effects above the spontaneous level were detected in human patients administered trimethoprim and the substance did not induce chromosomal damage in human lymphocytes *in vitro*. No oncogenicity studies with trimethoprim have been reported so the significance of the positive mutagenicity assays is not clear. However, no evidence of any preneoplastic effects was evident from the short term studies and the use of trimethoprim in human medicine has not been associated with any carcinogenic effect.

Trimethoprim adversely the fertility of female rats at high dose levels. At maternally-toxic dose levels it was teratogenic in the rat but not in the rabbit. The NOEL in rats was 28-30 mg/kg bw per day. Trimethoprim is contraindicated in human medicine during pregnancy because of its teratogenic potential though there is no evidence that terata have resulted from its use. One study reported reduced sperm counts in males administered trimethoprim.

3. In humans, trimethoprim has been reported to cause gastro-intestinal disturbances (nausea, vomiting), pruritis, rashes and depression of haematopoiesis. It may predispose to folate deficiency and is contraindicated in pregnancy, neonates and renal impairment.

4. The Committee for Veterinary Medicinal Products agreed that it would be inappropriate to estimate an acceptable daily intake for trimethoprim due to the lack of oncogenicity data and the evidence of mutagenicity in some studies.
5. The Committee for Veterinary Medicinal Products agreed that residues of trimethoprim in milk and meat (muscle, liver, kidney and fat) should be as low as possible. As 0.05 mg/kg appeared to be the lowest level consistent with the practical analytical methods available for residue analysis, the CVMP set the MRLs for milk and meat at this level. Taking into account good husbandry practice, residues of trimethoprim are expected to be below this level.

Trimethoprim is usually administered in combination with a sulphonamide but is excreted faster. Consequently if no residues of sulphonamide are detectable, no residues of trimethoprim would be expected.

6. A microbiological method using *Bacillus pumulis* has been developed (Sonnenshein et al, 1976). There are also GLC and HPLC methods available (Bye and Brown, 1977 and Nordholm and Dalgaard, 1984); the latter method includes determination of metabolites. Malish et al (1984) described a method for the simultaneous determination of residues of sulfonamides, nitrofurans, chloramphenicol and trimethoprim in foods of animal origin. The final extract was analysed by a combination of HPLC with UV detection and capillary GC; the trimethoprim was quantified by capillary GC using a thermionic detector.