The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DAPSONE (1)

SUMMARY REPORT

1. Dapsone, 4, 4'-diaminodiphenylsulphone (DDS) is used in human medicine in the treatment of leprosy and as an antimalarial drug. It has been used in the treatment of tuberculosis and of dermatitis herpetiformis.

   In veterinary medicine dapsone is used either alone or in combination with other chemotherapeutic agents, for the intramammary treatment of bovine mastitis, for the oral treatment of bovine coccidiosis and the intra-uterine treatment of endometritis.

2. Dapsone administered to rats causes haematological effects, increases in organ weights, degeneration of liver and spleen and hyperreactivity. Toxic effects of dapsone in humans indicate haemolytic anemia, leucopenia, gastro-intestinal and neurologic effects.

   Mutagenicity testing of dapsone, its N-acetylated and hydroxylated metabolites in bacterial and mammalian cells with and without metabolic activation indicate negative results.

   Carcinogenicity testing of dapsone in rats gives at high doses evidence of an increased incidence of tumors in the spleen and peritoneum of males and of thyroid tumors in both sexes; studies with mice gave no evidence for carcinogenicity.

   Epidemiological data on carcinogenicity of dapsone in humans are insufficient. Based on the results of short-term mutagenicity testing dapsone is considered as a carcinogen with a threshold level.

   The available toxicological information, originating mainly from extensive human use, indicates a NOEL of approximately 0-0.7 mg/kg bw/day based on the absence of haemolytic effects in glucose-6-phosphate-dehydrogenase deficient persons.

3. Dapsone exhibits a moderate anti-microbial activity. MIC-values for a large number of microorganisms have been determined varying between 0.5 → 128 µg/ml.

4. Human use of dapsone has been extensive but animal toxicity testing is incomplete. Therefore an additional safety factor of 200 is used for extrapolation of the existing toxicity data which results in a provisional ADI of 0-3.5 ug/kg bw.

5. Calculation of an MRL for residues of dapsone in milk is based on potential exposure of younger children whose diet may substantially be comprised of milk (1.5 l/day). Therefore an MRL for dapsone in milk of 3.5 x 10 x 2/3 - 25 µg/l has been adopted, and for meat a similar value.

6. A routine method for detection of antibiotics, sulfonamides and dapsone in test tubes of heat treated milk is being worked out under Council Directive 85/397/EEC (DG VI). The bio-assay is based on growth of *Bac. stearothermophilus var.calidolactis* spores in milk samples and has a detection limit of 15-20 ppb.

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A method using agar testplates with *Bac. subtilis* spores has a sensitivity of 10 ppb but needs further validation for routine screening (J F M Nouws et al, Vet. Quart. 7, 76-78). Two methods not suited for routine control but for confirmation are available :

- dapsone and its monoacetyl-derivative can be detected in milk and meat at a level of 10 ppb using continous flow technique and columnswitching HPLC (M M L Aerts and W M J Beek 1988. J. Chrom., 435, 97-112).
- a method for detection of dapsone and monoacetyldapsone based on solid phase extraction, derivatisation with fluorescamine and TLC has a sensitivity of 5 ppb (M M L Aerts and H J Keukens, RIKILT). This method has been transmitted to the EEC.

7. Results of additional studies establishing an NOEL in experimental animals should be provided before 1 January 1994 concerning potential reproductive and teratogenic effects.