European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

BITUMINOSULFONATES, AMMONIUM AND SODIUM SALTS
(**Extension to dairy cattle**)

SUMMARY REPORT (2)

1. Bituminosulfonates (ammonium and sodium salts of dark bituminosulfonate and ammonium salt of light bituminosulfonate) are used in veterinary medicine for their bacteriostatic properties in the treatment of inflammatory skin disorders in horses, pigs, cattle, rabbits and other animals. They are applied topically undiluted or in ointments at a concentration of 20 to50 %.

   Bituminosulfonates are also used in human medicine, in an oral preparation containing sodium bituminosulfonate which is intended for administration at a dose of 1200 mg per day, for 14 days, followed by a further 7 days on half-dose for the treatment of diseases such as acne, seborrhoea, rosacea and furunculosis. A wide range of topical preparations are also available, for the treatment of skin disorders such as eczema and psoriasis.

   Bituminosulfonates were previously assessed by the CVMP and a toxicological ADI of 1.65 mg/kg bw, i.e. 99 mg/person was established based on the NOEL of 330 mg/kg bw from the 6-month oral dog study and applying a safety factor of 200.

   Currently, bituminosulfonates, are included in Annex II of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Target species	Other provisions
Bituminosulfonates, ammonium and sodium salts	All mammalian food producing species	For topical use only. Not for use in animals from which milk is produced for human consumption

   An application has now been submitted for the extension of ammonium and sodium salts of bituminosulfonates to dairy cattle. The proposed indication for dairy cattle is inflammatory skin disorders, wounds. The products are in the form of ointments containing 10 to 50% bituminosulfonates for topical use only.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.eu.int http://www.emea.eu.int

2. A GLP-compliant *in vitro* study was carried out to investigate the transdermal penetration of dark sulfonated shale oil into bovine udders and thereby into milk after dermal application and systemic application. The study used isolated perfused bovine udder with viable status of the skin maintained for 8 hours by perfusion with tyrode solution. Residues were determined by measuring 3 arylsulfonic acids components and benzo[a]pyrene as an impurity. These 3 leading components were selected on account of their comparably high concentration. The limits of quantification were 50 µg/kg for the arylsulfonic acids and 0.008 µg/kg for benzo[a]pyrene. In the first part of the study a single topical application of 16 g over 400 cm^2 of skin /udder was administered to 3 udder halves. Perfusate samples and milk samples were taken before application and at 1, 2, 3, 4, 5, 6, 7 and 8 hours post application. In the second part of the study 20 mg/l of dark sulfonated shale oil was used as a perfusion liquid in a simulation of systemic administration in 2 udder halves. Milk samples were taken at the same time points in the first part. Results for arylsulfonic acid components and benzo[a]pyrene in all samples and at time points analysed, were found to be below the limits of quantification.

   The study is considered acceptable to demonstrate the very low absorption of the test substance following topical administration and to also demonstrate that the levels of residues in milk are below the limits of quantification. Assuming that absorption did occur, a worst case estimate of residues in milk was calculated as 2.7 mg bituminosulfonates in 1.5 kg of milk. The worst case estimate of consumer intake in the pig pharmacokinetic study was 2362 µg/day, therefore adding these 2 estimates would give a theoretical maximum consumer intake of 5062 µg/day which is 5.1 % of the ADI.

3. An analytical method was developed for the detection of the selected single components in bituminosulfonic acids in bovine milk from the *in vitro* study in udder tissue. HPLC was used for the separation and to determine the profile of components. GC/MS was used for the separation of the methylated arylsulfonic acids. The sulfonic acid methyl esters made up 22 % of the total mass and there were more than 80 single components characterised. To detect the 3 components in milk an enrichment and determination procedure was developed. 3-Methylthiosulphonic acid was chosen as an internal standard based on its retention behaviour. The extract of sulfonic acid methyl esters was purified by chromatography using partially deactivated silica gel. The fraction was analysed by gas chromatography using MS/SIM technique. The limit of detection was 15 µg/kg and the limit of quantification was 50 µg/kg.

Conclusions and recommendations

Having considered that:

- a toxicological ADI of 1.65 mg/kg bw was previously established,
- the product is intended for topical application only,
- dermal absorption was only 1 to 3% after a 24 hour application in the pig,
- elimination was rapid after oral administration with little evidence of bioaccumulation,
- bituminosulfonate components or impurities were not detected in milk in *in vitro* studies simulating dermal and systemic application to cow's udders,
- the worst case estimate of consumer intake from porcine tissues and bovine milk at a zero withdrawal period would be 5.1 % of the ADI.

the Committee for Medicinal Products for Veterinary Use considers that there is no need to establish an MRL for bituminosulfonates, ammonium and sodium salts in milk and recommends the modification of the current Annex II of Council Regulation (EEC) No 2377/90 for the substance in accordance with the following table:

Pharmacologically active substance(s)	Target species	Other provisions
Bituminosulfonates, ammonium and sodium salts	All mammalian food producing species	For topical use only