



## COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

### **BISMUTH SUBNITRATE** (Extension to intramammary administration)

#### SUMMARY REPORT (2)

1. Bismuth subnitrate is an inorganic salt of bismuth. Bismuth is a non-essential trace element with an estimated normal daily intake in humans between 5 and 20 µg.

Inorganic bismuth compounds including bismuth subnitrate are used orally in veterinary and human medicine for their antacid action and for their mild astringent action in gastrointestinal disorders including diarrhoea, flatulence and ulcerative gastritis and colitis.

Bismuth subnitrate had previously been assessed by the Committee for Veterinary Medicinal Products and is included in Annex II of Council Regulation (EEC) No 2377/90 for all food producing species in accordance with the following table:

Pharmacologically active substance	Animal species	Other provisions
Bismuth subnitrate	All food producing species	For oral use only

An application has now been submitted for an extension of the MRL-evaluation for bismuth subnitrate to intramammary use in dairy cows. Bismuth subnitrate is indicated to provide protection against mastitis in dry cows by single intramammary administration via the teat duct at drying-off at a dose of 4 g per quarter (2.68 g bismuth subnitrate).

2. In general, the composition of bismuth salts is variable. For bismuth subnitrate most often  $(\text{Bi}_2\text{O}_3)_6(\text{N}_2\text{O}_5)_5(\text{H}_2\text{O})_9$  is encountered, and both light and heavy forms exist: the light form is a mixture of bismuth subnitrate and bismuth subcarbonate ( $\text{BiO}_2\text{CO}_3$ ) in a ratio of either 20:80 or 80:20 and contains 73 to 80% bismuth, whereas the heavy form consists of the subnitrate only and contains 72% bismuth.
3. Systemic absorption is not necessary for activity of inorganic bismuth compounds as their site of action is at the site of administration. Protection against mastitis at drying-off is caused by physically sealing the teat duct with insoluble bismuth subnitrate.
4. The gastrointestinal absorption of bismuth from bismuth subnitrate and other bismuth compounds shows a large inter-individual variation. Bismuth salts such as bismuth subnitrate, subcarbonate, subgallate and subsalicylate are only slightly, if at all, absorbed after oral intake. Absorption can be enhanced by simultaneous intake of citrate and sulfhydryl-group-containing compounds. In general, the bioavailability of bismuth and bismuth salts is very low (far less than 1%) in experimental animals and humans. For bismuth subnitrate an oral bioavailability in humans of less than 0.005% is reported.

Reported endogenous bismuth blood levels in humans range between 1 and 15 µg/l and are known to be highly variable. These levels remained unchanged by oral administration of therapeutic doses (approximately 5 to 30 mg/kg bw/day) in man. The distribution of bismuth in the tissues is largely independent of the bismuth compound administered or the route of administration. Highest concentrations are found in kidney, lower levels in lung, spleen, liver, brain, bone and muscle. In the kidney bismuth is retained longer than in any other organ.

No metabolism of bismuth is known. In the kidney, it induces the *de novo* synthesis of a bismuth-metal-binding protein, a kind of methallothionein.

Ingested bismuth is largely eliminated unabsorbed via faeces. Absorbed bismuth is eliminated from the body by both the urinary and the faecal (including bile) routes.

Although pharmacokinetic or residue data after oral use of bismuth subnitrate in target animals were not available, from the available data in experimental animals and humans it is plausible that the oral absorption of bismuth subnitrate in target animals will also be negligible. Hence, the presence of bismuth residues in edible products of target animals is extremely unlikely.

5. Only a few oral toxicity studies with bismuth compounds have been reported in literature. In early carcinogenicity studies, insoluble bismuth subcarbonate (1000 mg/kg bw/day to rats), bismuth subchloride (500 to 2500 mg/kg bw/day to rats) and bismuth dimethyldithiocarbonate (5 mg/kg bw/day to mice) in feed had no carcinogenic potential. In bacteria, no mutagenic potential was observed for bismuth bromide. In an *in vivo* mutagenicity study, oral intake of bismuth oxide (up to 1000 mg/kg bw/day) resulted in an increase in chromosomal aberrations in mouse bone marrow after 21 days of treatment, but not after 7 and 14 days of treatment. The carcinogenicity and mutagenicity studies were of poor quality and few details were reported.

More information is available in literature on adverse effects in humans because bismuth-containing medications are used worldwide in large amounts in often uncontrolled situations. The risk for bismuth-related toxicity in the population is very low. Bismuth toxicity develops only from excessive dosage (ingestion of bismuth over a prolonged period of time or intramuscular injections) and is characterised by nephrotoxicity, osteoarthropathy, encephalopathy, hepatotoxicity, stomatitis and gingivitis. The insoluble inorganic bismuth compounds are reported to be mainly associated with reversible encephalopathy.

8. Bismuth levels in milk from cows treated at drying-off with a product intended for sealing the teat canal at the recommended dose were measured using a partly validated analytical method. The highest individual bismuth concentration at the 9<sup>th</sup> milking was 616 µg bismuth/kg milk and the levels decreased thereafter. The concentrations in milk were independent of the drying-off period.

## Conclusions and recommendation

Having considered the criteria laid down by the Committee for inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- bismuth subnitrate intramammary is used for infrequent treatment (once a year),
- the animals are unlikely to be sent for slaughter immediately after treatment and/or calving,
- the first 6 to 8 milkings after calving are colostrum,
- bismuth is a normal component of the human diet,
- systemic availability after intramammary administration is unlikely,
- although it is noted that the maximal daily intake in man, resulting from the recommended treatment cannot be determined with certainty, due to an incomplete validation of analytical methods in the residue studies, it is clear that bismuth subnitrate is virtually not absorbed from the gastrointestinal tract;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for bismuth subnitrate after intramammary use and recommends its inclusion in Annex II to Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Bismuth subnitrate	Bovine	For intramammary use only