

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BISMUTH SUBNITRATE BISMUTH SUBCARBONATE BISMUTH SUBGALLATE BISMUTH SUBSALICYLATE

SUMMARY REPORT (1)

1. Bismuth compounds such as bismuth subnitrate, subcarbonate, subgallate and subsalicylate are used orally in veterinary and human medicine for antacid action and for mildly astringent action in gastrointestinal disorders including diarrhoea, flatulence and ulcerative gastritis and colitis.

Bismuth subnitrate is indicated in most animal species (small and large cattle, swine, sheep, goats and horses) at oral doses of 0.45-3 g/day (approximately 6-15 mg/kg bw/day, depending on size and weight of the animal) for several days.

In human medicine, the recommended oral dosage for the different bismuth salts (expressed as bismuth) is 100-450 mg (approximately 5-30 mg/kg bw/day) 3-4 times a day for several days/weeks.

2. Bismuth subnitrate, subcarbonate, subgallate and subsalicylate are salts of bismuth. Bismuth is a non-essential trace element, of which the normal daily intake in humans is estimated to be between 5 and 20 µg. 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 subcarbonate in a ratio of either 20:80 or 80:20 and contains 73-80% bismuth, whereas the heavy form consists of the subnitrate only and contains 72% bismuth. Bismuth subcarbonate (BiO_2CO_3), bismuth subgallate ($\text{C}_7\text{H}_5\text{BiO}_6$) and bismuth subsalicylate ($\text{HOC}_6\text{H}_4\text{COOBiO}$) contain 82%, 53% and 58% bismuth, respectively.
3. Systemic absorption is not necessary for activity of inorganic bismuth compounds as their site of action is within the gastrointestinal lumen. The exact mechanism of action is unknown, but the therapeutic activity might result from mucosa-protective properties, and from inhibition of colonic bacteria acting on fermentable food residues.
4. The gastrointestinal absorption of bismuth from bismuth subnitrate and other bismuth compounds shows a large interindividual 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 (less than 1%) in experimental animals and humans. For bismuth subgallate, a human oral bioavailability of 0.04% is reported, and for bismuth subnitrate and subsalicylate even less (less than 0.005%).

Reported endogenous bismuth blood levels in humans are between 1 and 15 µg/l and are known to be highly variable. These levels remained unchanged by oral administration of therapeutic doses in man. The distribution of bismuth over the tissues is largely independent of the bismuth compound administered or the route of administration. The highest concentration is found in kidney and lower levels in lung, spleen, liver, brain, bone and muscle. The retention time of bismuth in the kidney is 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 metallothionein.

Ingested bismuth is largely eliminated unabsorbed via faeces. Absorbed bismuth is eliminated from the body by both the urinary and 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 (as well as that of bismuth subcarbonate, subgallate and subsalicylate) 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), subchloride (500-2500 mg/kg bw/day to rats) and 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 characterized by nephrotoxicity, osteoarthropathy, encephalopathy, hepatotoxicity, stomatitis and gingivitis. The insoluble inorganic bismuth compounds are reported to be mainly associated with reversible encephalopathy.

Conclusion and recommendation

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

- bismuth subnitrate, as well as bismuth subcarbonate, subgallate and subsalicylate, are used in a small number of animals for non-regular treatment;
- the animals are unlikely to be sent for slaughter immediately after treatment;
- bismuth is a normal component of the human diet ;
- bismuth subnitrate, subcarbonate, subgallate and subsalicylate are virtually not absorbed from the gastrointestinal tract,

the Committee considers that there is no need to establish an MRL for bismuth subnitrate, subcarbonate, subgallate and subsalicylate and recommends their inclusion into Annex II of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Bismuth subnitrate	All food producing species	For oral use only
Bismuth subcarbonate	All food producing species	For oral use only
Bismuth subgallate	All food producing species	For oral use only
Bismuth subsalicylate	All food producing species	For oral use only