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

EMEA/MRL/182/97-FINAL
March 1997

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BROMIDE, SODIUM SALT

SUMMARY REPORT

1. Sodium bromide can be used in iodophor teat dip formulations as a means of stabilising the iodophor and controlling degradation reactions with organic carrier materials. Sodium bromide has been used in iodophors at concentrations of 29-42 g/kg in the concentrated product, which was recommended to be diluted to give concentrations of 1.1-1.2 g/kg (equivalent to approximately 900 mg/litre of bromide ion) in the teat dip. In addition to being used as teat dips to prevent mastitis, iodophors can be used more generally as disinfectants. Historically, bromides of ammonia, potassium, sodium and strontium have been used widely in human medicine as sedatives, and anticonvulsants at adult doses of up to 6 g/person/day (100 mg/kg bw/day), but they are no longer recommended.

2. Bromide is readily absorbed passively from the gut in humans by the paracellular pathway. Plasma bromide concentration initially rises rapidly and reaches a plateau after 3 weeks. The plateau concentrations of bromide in serum, kidney and brain are directly proportional to the dietary concentrations administered. Bromide is distributed mainly in the extracellular fluid with a volume of distribution of approximately 0.3 litre/kg. It can penetrate the blood-brain barrier. It can cross the placenta to the foetus more readily than it can be eliminated by the foetus back to the maternal blood. Thus there is a potential for accumulation in the foetus, and there have been human cases of congenital bromism. Bromide can also pass into breast milk. Bromide is also actively secreted into saliva, and salivary-gastroenteric circulation occurs. Excretion of bromide is mainly via the kidneys, where the bromide competes with chloride for tubular reabsorption. The plasma half-life is 3 days in rats and 10-12 days in humans. Clearance in the rat is low at 2.5 ml/hr./kg. In rats fed a chloride-deficient diet the clearance of bromide is reduced to 0.3 ml/hr./kg and the plasma half-life is extended to 25 days.

3. The pharmacological and toxicological effects of bromide are related to it displacing other halides in biological systems: chloride in the blood and central nervous system; iodide in the thyroid. There is competition between bromide and iodide for uptake into thyroid tissue, but bromide unlike iodide cannot be incorporated into the thyroid hormones T4 and T3 as it is not oxidised by thyroid peroxidase.

4. The bromide ion is of low acute oral toxicity. The single dose oral LD_{50} of sodium bromide in rats was 3500 mg/kg bw. Mouse LD_{50} values of 5020 mg/kg bw (subcutaneous) and 7000 mg/kg bw (oral route) have been reported for sodium bromide.

5. The toxicity of sodium bromide was low in a 4-week feeding study in female rats. No adverse effects were seen at doses of up to 4800 mg/kg of sodium bromide (i.e. 287 mg Br^-/kg bw/day). At 19200 mg/kg of sodium bromide (i.e. 1580 mg Br^-/kg bw/day), there was reduced grooming, motor incoordination of the back legs and increased relative kidney weight.

6. In a 90-day feeding study, no adverse effects were seen in female rats given up to 300 mg/kg of sodium bromide in their diets (equivalent to 14.0 mg Br^-/kg bw/day) nor in males given up to 1200 mg/kg (80.6 mg Br^-/kg bw/day). At higher doses there were increases in the weights of the thyroid, adrenals and prostate which were matched by histological evidence of increased secretory activity of these organs. High doses also produced decreased spermatogenesis in the testes or a decreased number of corpora lutea in the ovaries, along with more general signs of toxicity such as poor grooming, motor incoordination and growth retardation. There was also an increased neutrophil count.

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.eudra.org http://www.eudra.org/emea.html

7. In a second 90-day feeding study using only male rats, no adverse effects were seen at dietary concentrations of up to 300 mg/kg of sodium bromide (approximating to 12 mg Br^-/kg bw/day). The effects seen at higher doses were similar to those seen in the first 90-day study. Measurement of serum hormone levels showed T4 to be reduced at doses of 1200 mg/kg (47 mg Br^-/kg bw/day) or more. Growth hormone, corticosterone and testosterone were decreased; and TSH, thyrotropin releasing hormone, insulin and FSH were increased at 19,200 mg/kg of sodium bromide (746 mg Br^-/kg bw/day).

8. In a three generation rat reproduction study, decreases in serum T4 were detected at all dietary concentrations of sodium bromide which were tested: i.e. down to 75 mg/kg (approximately 2.9 mg Br^-/kg bw/day), although the T4 decreases of less than 20% seen at doses of 300 mg/kg (approximately 12 mg Br^-/kg bw/day) or less were considered to be too small to have any adverse effect on health. At the two highest doses of 4800 mg/kg (186 mg Br^-/kg bw/day) and 19200 mg/kg (746 mg Br^-/kg bw/day), the fertility of both male and females was decreased. At the highest dose, there was an increased neutrophil count and a decreased lymphocyte count. It was confirmed that bromide crossed the placenta to the foetuses, but there was no evidence of mortality to embryos or foetuses and examination of the pups at birth showed no gross malformations. A no-adverse-effect level of 300 mg/kg (12 mg Br^-/kg bw/day) was indicated by the results of this study.

9. In a behavioural study in mice, motility and evasion time were adversely affected when mice were fed 1200 mg/kg of sodium bromide (approximating 47 mg Br^-/kg bw/day) or more. No effects were seen at 400 mg/kg (15 mg Br^-/kg bw/day).

10. No mutagenicity was detected in limited Ames tests on sodium bromide and on ammonium bromide in *Salmonella typhimurium* strains TA98 and TA100, with and without metabolic activation.

11. There were no carcinogenicity studies.

12. Animals fed with feeds which had been treated with methyl bromide and contained residues of inorganic bromide showed signs of toxicity which were similar to those seen with sodium bromide. No adverse effects were seen at the following dosages: dogs fed up to 75 mg Br^-/kg bw/day for 12 months (ill effects at 100 mg Br^-/kg bw/day); rats fed up to 60 mg Br^-/kg bw/day for 12 months (ill effects at 575 mg Br^-/kg bw/day); rabbits fed up to 2.5 mg Br^-/kg bw/day for 12 months (ill effects at 100 mg Br^-/kg bw/day).

13. In the past, bromides were used in human medicine as sedatives and in the treatment of epilepsy at doses of up to 6 g/person/day. Doses of bromide giving plasma levels of 12 mmol/litre (96 mg Br^-/litre) or more produced bromism, and plasma concentrations greater than 40 mmol/litre (320 mg Br^-/litre) were sometimes fatal. The results from a series of studies in human volunteers given oral sodium bromide showed small changes in the serum levels of total T4 and free T4 were increased at the highest dose tested: effect at 9 mg Br^-/kg bw/day but not at 7 mg Br^-/kg bw/day. Effects on electroencephalograph (EEG) measurements gave the most sensitive indicator of bromide toxicity. The specific types of EEG changes were not consistent between experiments and their clinical significance is not clear. The results did however indicate an NOEL of 4 mg Br^-/kg bw/day for humans.

14. An ADI of 0.4 mg/kg bw (0-24 mg/person) can be set for inorganic bromide, by application of a safety factor of 10 to the NOEL of 4 mg Br^-/kg bw/day taken from human studies. The available animal studies were less sensitive to the adverse effects of bromide than the human studies which took EEG measurements. The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) had set a higher ADI of 0-1.0 mg/kg bw for inorganic bromide. The JMPR took account of the human study which was used as the basis of the proposed European ADI, but at the time of the JMPR assessment the result of this study was regarded as provisional and in need of confirmation. Since the JMPR assessment this result has been confirmed in a second human study and it is now appropriate to set the ADI on the basis of the NOEL of 4 mg Br^-/kg bw/day from human studies.

15. No measurements have been made of the depletion of bromide residues from tissues and milk following the use of bromide-containing iodophor teat dips. However, it has been estimated by extrapolation from the carry over into milk of iodine from teat dips that use of bromide in iodophor teat dips may contribute up to 772 mg/litre of sodium bromide to milk, which is equivalent to 595 mg/litre of bromide ion (i.e. about 0.6 mg/litre). In a worst case situation, a person drinking 1.5 litres of milk per day could therefore be exposed to up to 0.9 mg Br^-/person/day as a result of the use of bromide in teat dips.

16. Market basket surveys sponsored by the Netherlands government have shown that consumers are exposed to up to 13.4 mg Br^-/person/day (with mean intakes estimated to be in the region of 8.4 to 9.4 mg Br^-/person/day) from other dietary sources of bromide. MRLs recommended by Codex allow concentrations of 20-400 mg/kg of bromide ion in various foodstuffs, and EU regulations set an MRL of 50 mg/kg for inorganic bromide in cereals.

Conclusions and recommendation

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

- is a normal component of the diet in humans;
- the estimated extra consumer intake of bromide resulting from the use as teat dip is very small compared with the intake of bromide of bromide from other dietary sources and will not have any adverse effect on the health of the consumers;

the Committee considers that there is no need to establish an MRL for sodium bromide and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/900 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Bromide, sodium salt	All food producing mammals	For topical use only