The European Agency for the Evaluation of Medicinal Products

EMEA/CVMP/025/MRL

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BORIC ACID AND BORATES

SUMMARY REPORT

1. Boric Acid is used widely for both medicinal and non-medicinal purposes. It is the ingredient in many cosmetics, pharmaceuticals and pesticides. In pharmaceuticals it is used as preservative, antiseptic, water softener, pH adjuster, emulsifier, neutralizer, stabilizer, buffer or viscosifier. Other applications include its use in food packaging and as an insecticide or fungicide.

2. The acute oral and parenteral toxicity of Boric acid is low. Acute oral LD50 values in rats exceed 3g/kg bodyweight. LD50 following i.v. administration to rats is 1.3g/kg bodyweight; LD50 for rabbit following i.v. administration is 800 - 900 mg/kg bodyweight. The signs of toxicity included depression, ataxia, convulsion and death.

3. Chronic oral toxicity studies in male rats and dogs indicated that a diet containing a concentration 1170 ppm boron equivalence of Boric acid (approximately 668.6 mg/kg/day boric acid for rats and 501.4 mg/kg/day boric acid for dogs) for two years induced testicular atrophy. The dogs showed no other signs of toxicity. The rats receiving this dose had coarse hair coats, postural abnormalities, swollen pads, inflamed eyelids, reduced food consumption, retarded growth and haematological disturbances. A no-effect-level of 100 mg/kg bodyweight/day was established for rats while a no-effect-level for dogs was 50 mg/kg bodyweight/day.

4. In a variety of genotoxicity tests with prokaryotic and eukaryotic cells, boric acid was found to be uniformly non-mutagenic. Boric acid also did not induce sister-chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells. All assays were performed with and without metabolic activation.

5. In a two year field study in mice, boric acid showed no evidence of carcinogenicity at doses of 2,500 or 5,000 ppm.

6. In rat reproduction studies, doses of 1170 ppm were found to interfere with reproduction, while doses of 350 ppm had no adverse effects on fertility, lactation, litter size, weight or appearance. Decreased feed intake and vaginal bleeding associated with abortion were the signs of intoxication of rabbits treated orally with 250 mg boric acid/kg bodyweight on gestation day 6 - 19. The same doses was associated with severe developmental toxicity (prenatal mortality, malformations). No definitive effects were observed at 125 mg/kg bodyweight per day.

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7. The minimum lethal dose of ingested boric acid in man has not been precisely determined but is approximately 2 - 3 g in infants, 5 - 6 g in children and 15 - 20 g in adults. Under certain instances systemic toxicity has resulted from ingestion of as little as 0.17 - 0.2 g boric acid/kg bodyweight.

8. Boric acid is poorly absorbed through intact skin. It is absorbed through braided, denuded or burnt skin and some mucosal surfaces both in animals and man. It is excreted in the urine, faeces, saliva, milk and perspiration. Intestinal absorption of borine is rapid and almost complete. After ingestion of boric acid, peak blood concentrations being reached within 2 hours. In animals, the administered boric acid is distributed to all tissues. Pharmacokinetic studies in humans given a single 600 mg dose of boric acid by i.v. infusion, indicated rapid removal of boron and no tendency to accumulation. The elimination half/life of blood boron was approximately 21 hours. However, when repeated daily doses of 200 mg/kg were given subcutaneously, 14 - 18 days were required before urinary excretion reached the plateau. This together with the fact that boric acid can still be found in the brain of animals four days after the discontinuation of a series of doses, indicates cumulative action.

9. Boron, the principle component of boric acid, is an essential element of plant food and occurs in vegetable food and in water. Mushrooms contain 31 - 80 mg/kg boron, brassicas 10 - 145 mg/kg; quinces 85 - 160 mg/kg and strawberries 45 - 160 mg/kg. The average daily intake of boron in France has been estimated at 25 mg/person per day, but with variations over very large limits: minimum 3.5 mg of boron per day - maximum 41 mg of boron per day.

10. Many farm animals, being herbivores consume boron daily. Indeed tissues from untreated sheep contain residues of boron of 2 - 32 mg/kg.

11. The amount of boric acid to which the consumer may be exposed from the use of veterinary medicinal products relates to use as a constituent in cotton bandages and in large volume parenteral solutions.

12. In a bioavailability study in horses treated with one to eight poultices containing 0.432g boron per dressing, the highest concentration detected in plasma was approximately 8 mg/l; 7 days after removal of last poultice concentrations were 1 mg/l or less. Normal boron levels range from 0.1 - 0.44 mg/l. Assuming that 0.432g is totally absorbed from a pad in a pony of 250 kg, and that boron is evenly distributed through all tissues, the maximum residue to which a consumer will be exposed is 2 mg/kg horsemeat/day.

13. In a study on lactating dairy cows given a single subcutaneous injection of 27g boric acid, boron levels in milk increased from a mean of 1.6 mg/ml pre-treatment to 3.43 mg/ml at 12 hours before decreasing to 2.65 mg/ml at 24 hours. Assuming boron was evenly distributed throughout the tissues, 0.5 kg of meat and offal would contain :

$$\frac{27}{400\ (a)} \text{ X } 0.5 = 0.034\text{g} = 34\text{ mg}$$

(a) bodyweight of cow

This assumes that animals were slaughtered immediately after treatment and thus does not consider elimination from treated animals which is rapid and effective.

14. The theoretical maximum dose to which a consumer could be exposed is 39 mg/person and is within the range normally ingested by man. It includes a contribution from meat and offal of 34 mg and a contribution from milk of 5 mg.

Having considered that:

· boron is a normal component of the diet in humans;

· boric acid will be used in individual animals;

· boric acid is rapidly excreted;

· the theoretical maximum amount of boron from tissues of treated animals to which the consumer may be exposed is within the range which may be ingested daily from all sources of food and drink;

The Committee considers that no Maximum Residue Limits are necessary for these substances and recommends the inclusion into Annex II of Council Regulation (EEC) No 2377/90 of Boric acid and borates for all food-producing animals in accordance with the following table.

Pharmacologically active substance(s)	Animal species	Other provisions
Boric acid and borates	All food-producing species	