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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

SODIUM CHLORITE

SUMMARY REPORT

1. Sodium chlorite is used in veterinary medicine as a medical disinfectant in post-milking teat dip products used topically for the control of mastitis in dairy cattle.

2. When sodium chlorite (Na ClO_2) is mixed prior to use (in the formulated product) a chemical equilibrium is established containing

   chlorous acid ($HClO_2$) which degrades to chlorine dioxide (ClO_2 a gas), and to a lesser extent sodium chlorate ($NaClO_3$). The chlorate (ClO_3) eventually degrades to ClO_2 and NaCl as major products. The chlorous acid and chlorine dioxide are responsible for the microbicidal action of the product, via non-specific oxidative damage to bacterial membranes.

3. In general, the toxicity studies presented were not conducted to current scientific protocols, and clear NOEL's were generally not established for each compound, however all three compounds (chlorine dioxide, sodium chlorite and sodium chlorate) tended to produce the same pattern of toxicity.

4. Chlorine dioxide, sodium chlorite and sodium chlorate were all shown to be well absorbed by the oral route in rats, by using radiolabelled compounds (C_{max} around 1-2 hours). The plasma elimination half lives ranged from 35 to 44 hours. The main route of excretion for sodium chlorite and chlorine dioxide appeared to be via the kidneys, predominantly as chloride (32 % and 27 % of the dose respectively at 72 hours), with some chlorite (6 % and 3.5 % of the dose respectively at 72 hours), and a little chlorate (0.73 % of the dose at 72 hours). For sodium chlorite, 83 % of the recovered dose was found in urine, and 13 % in faeces. For chorine dioxide and sodium chlorate no radioactivity was detected in expired air.

5. Repeat-dose toxicity tests with chlorine dioxide, sodium chlorite and sodium chlorate all produced a similar spectrum of dose-related toxic effects in various animals species (rat, mouse, rabbit, African green monkey). The main effect was on haematological parameters (reduced glutathione concentration, reduced erythrocyte counts, reduced PCV, reduced haemoglobin concentration, reduced osmotic fragility of erythrocytes, haemolysis, methaemoglobin formation) which was observed in rats and mice. Inhibition of thyroid hormone synthesis was observed in rats and African green monkeys with chlorine dioxide (9 mg/kg bwt/day in drinking water), which was dose-related and reversible on cessation of treatment. A NOEL of 3 mg/kg/day was established for chlorine dioxide which did not affect serum thyroxine levels, whereas both sodium chlorite and sodium chlorate had no effect on thyroid function in monkeys at doses of 60 mg/kg bw/day for 30-60 days.

6. Overall, studies with chlorine dioxide, sodium chlorite and sodium chlorate suggest that they are not teratogenic in mice, rats or rabbits. At high doses of chlorine dioxide and sodium chlorite (100 mg/l of drinking water) the number of implants and live foetesus per dam tended to be reduced, and foetal weight and length and pup weight were decreased. At lower doses (10 mg/l of drinking water) there were no effects on female fertility, gestation length, litter size and weight.

   Male fertility was unaffected by chlorine dioxide, but sperm development was affected after treatment with 100 mg/l of sodium chlorite. Exposure of the pups to both chlorine dioxide and sodium chlorite resulted in reduced thyroid hormone levels (T_3 and T_4) and inhibition of locomotor activity, suggesting delayed neuro-behavioural development in young animals.

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7. Conflicting results have been produced in the mutagenicity tests conducted with chlorine dioxide, sodium chlorite, and sodium chlorate. Sodium chlorite was positive in two separate Ames tests, an *in vitro* chromosomal aberration test, and an *in vivo* mouse micronucleus test after intraperitoneal dosing. In contrast, it was non-mutagenic in a mouse micronucleus test when administered orally, and also negative in a test to assess sperm-head abnormalities induced in mice after oral treatment.

   Chlorine dioxide was reported to be positive in an Ames test in only one strain out of 6 (TA100), but negative in an *in vitro* chromosome aberration test in Chinese hamster fibroblasts. *In vivo*, two mouse micronucleus studies were conducted, resulting in one positive and one negative result. Chlorine dioxide also did not induce sperm head abnormalities in mice.

   Sodium chlorate was positive in two separate Ames tests with metabolic activation, and in a Drosophila recessive lethal mutation test. It was negative in two mouse micronucleus tests and in a bone marrow chromosomal aberration assay.

   However, these conflicting mutagenicity results were considered of limited relevance since consumer exposure to residues in milk is extremely low compared to exposure via drinking water.

8. Classical carcinogenicity studies have not been conducted with sodium chlorite, however chronic studies have been performed where sodium chlorite was administered via drinking water at doses up to 0.05% in mice for 80 weeks and 0.06% in rats for 85 weeks. The survival rate and incidence of tumours were not significantly different between treated and control groups. Conventional carcinogenicity studies have not been conducted with chlorine dioxide or sodium chlorate, however, the data that are available do not suggest a significant carcinogenic hazard.

9. Data are available from a clinical trial in humans exposed to 500 ml of 5 mg/kg sodium chlorite (equivalent to 0.036 mg/kg bw) daily for 12 weeks, and also a prospective epidemiological study where 198 individuals were exposed for three months to chlorinated water with a mean chlorite concentration of 5 mg/l, and compared with 112 non-exposed individuals. In both studies there was no evidence of any overt toxicity as indicated by an extensive battery of biochemical and haematological tests and physical examination.

10. Chlorine dioxide, sodium chlorite and sodium chlorate are all present in drinking water which has been disinfected by chlorination processes.

    A considerable amount of data has been reviewed by various authorities regulating water quality, including WHO and U.S EPA, and regulatory limits have been proposed of 0.21 to 0.5 mg/l for chlorine dioxide and 0.024 to 0.5 mg/l for chlorite and chlorate in drinking water.

11. No specific pharmacokinetics studies have been performed in the target species, although dermal absorption in rats and absorption via the teat canal in cattle have both been shown to be negligible.

12. Milk collected in the normal way from treated cattle (even without udder washing), and also directly by catheterisation of the teat canal, has been shown not to possess antimicrobial activity when tested with *Bacillus stearothermophilus* (limit of detection 3 mg/l, although no validation data were provided for this method).

13. Residues of chlorite and chlorate in milk from cows treated with the formulated product tended to be below the limit of detection of 0.1 mg/l for the HPLC analytical method.

14. Transfer studies using chromium (III) oxide (Cr_2O_3) as an analytical marker have indicated that less than 0.025% of the applied formulated product is transferred to milk. On this basis, the maximum level of chlorite present in the milk (based on 0.32 % $NaClO_2$ present in the product, and assuming no degradation) would be 8 g (total dip used) x 0.025 % (degree of transfer) x 0.32%/14.4 kg (of milk), or 0.00044 ppm (0.44 µg/l).

15. When these residues data are compared with the regulatory limits set for water quality of 0.21 - 0.5 mg/l for chlorine dioxide and 0.024-0.5 mg/l for chlorite and chlorate, it can be seen that the

use of sodium chlorite as a teat dip does not present a risk to human consumers of milk from treated cows.

16. Consequently, it is recommended that an MRL is not required for sodium chlorite and that it should be entered into Annex II of Council Regulation (EEC) N° 2377/90.