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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

SUMMARY REPORT

CHLOROCRESOL
(4-chloro-3-methylphenol)

1. Chlorocresol is the International Non-proprietary Name (INN) for 4-chloro-3-methylphenol. It is also known as p-chloro-m-cresol. It is a potent disinfectant and antiseptic. It is used as a preservative in cosmetics and in human and veterinary medicinal products. In veterinary medicine it is used as an active ingredient in some preparations intended for topical use and as an excipient (preservative) in some preparations intended for oral and parenteral use. The normal concentration in veterinary products intended for both oral and parenteral use is 0.1-0.2%, but higher concentrations (up to 0.5%) may be present in topical preparations.

2. Chlorocresol shows antimicrobial activity against gram positive and gram negative bacteria and fungi. It is bacteriostatic at the concentrations (0.1 - 0.2%) normally employed in pharmaceutical products. No other significant pharmacological properties have been reported.

3. After oral administration of 300 mg/kg bw chlorocresol to male rats, the majority of the administered dose was excreted within 24 hours. Over this period, a mean of 67.2% of the dose was recovered from the urine and 0.4% from the faeces. Small amounts continued to be excreted in the urine for up to 72 hours but no further material was detected in faeces. In addition to chlorocresol, 2 polar metabolites were found in the urine but were not identified. No metabolites were found in faeces.

4. The absence of accumulation in tissues was confirmed in a 90-day repeated dose study in which concentrations of 0, 150, 500 or 1500 ppm chlorocresol were administered in the diet. After 1, 4, 8 and 13 weeks, the residues of unmetabolised chlorocresol were determined in the liver and fat tissue of 3 rats from each group. No samples contained residues above the limit of detection, 1.4 ng/kg.

5. Chlorocresol was of low acute toxicity *via* the oral route. Acute oral LD_{50} of 5129 and 3636 mg/kg bw were reported for male and female Sprague-Dawley rats respectively. The acute oral LD_{50} in male Wistar rats was 1830 mg/kg bw. Acute subcutaneous LD_{50} of 360 and 400 mg/kg bw were reported for mice and rats respectively.

6. In a published report, brief details of a repeat-dose study were provided, chlorocresol was administered by oral gavage to groups of rats at dose levels of 0, 50, 200 or 400 mg/kg bw per day for 28 days. Bodyweight gains were significantly reduced in both sexes at the top dose. There were no significant changes in the haematology and clinical chemistry values which were measured. At termination, there were no effects on organ weight and no gross- or histo-pathological changes attributable to treatment. The NOEL was 200 mg/kg bw/day.

7. Concentrations of 0, 150, 500 or 1500 ppm chlorocresol were administered in the diet to groups of rats (20/sex) for 90 days. The dose levels were equivalent to approximately 0, 7.5, 25 and 75 mg/kg bw/day. Bodyweight gain was reduced in male rats given 500 and 1500 ppm. There were no substance-related effects on clinical chemistry or haematology values. There were no gross- or histo-pathological changes attributable to treatment. The NOEL was 150 ppm, equivalent to approximately 7.5 mg/kg bw per day.

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8. Groups of 10 male and female New Zealand White rabbits were given daily topical doses of 0, 10, 40 or 160 mg/kg bw per day chlorocresol, 5 days per week, for 3 weeks. Signs of skin irritation were observed in the groups receiving 40 and 160 mg/kg bw. However there was no evidence of systemic toxicity at any dose level.

9. No information was provided concerning the reproductive toxicity of chlorocresol. However the chemically-related substance, phenol, was not teratogenic in the rat or mouse though high oral doses caused maternal and foetal toxicity. A Collaborative Perinatal Study found no association between the use of phenol as a food additive during the first 4 months of pregnancy and subsequent birth defects in human infants.

10. Concentrations in the range 1.28-800 µg/plate of chlorocresol were not mutagenic in an *in vitro* assay for gene mutation in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, in either the presence or absence of metabolic activation. A second *in vitro* bacterial mutation assay using the some strains and concentrations up to 500 µg/kg of chlorocresol also gave negative results. An *in vivo* micronucleus test was carried out in which male and female mice were given 2 doses of 200 or 400 mg/kg bw chlorocresol, 24 hours apart and killed 5 hours after the second dose; there was no increase in micronucleated PCEs at either dose. In a second *in vivo* assay in mice, 1.6 mg/kg bw/day of chlorocresol was administered intraperitoneally for 5 consecutive days. Thirty five days after administration, the contents of the vas deferens, epididymides and caudae were examined. There was no significant increase in the incidence of sperm head abnormalities whereas the cyclophosphamide positive control induced a significant increase in abnormalities.

11. No reports of carcinogenicity studies were provided. Because of the negative results in mutagenicity studies, carcinogenicity studies were not required.

12. *In vivo* MIC values were determined for chlorocresol against human strains of a number of bacteria and fungi. The study included some bacteria which may be found in the human gut flora; these were *Streptococcus faecium, Staphylococcus* spp and *Pseudamonas* spp. The MICs were in the range 800-3200 µg/ml. Chlorocresol was shown to be inactivated by contact with organic matter and under conditions of increasing pH.

13. Chlorocresol was a potent sensitizer in the guinea pig Maximization test of Magnusson and Kligman at the day 21 challenge. Two weeks later, the reactivity was significantly decreased. Humans are rarely sensitized by chlorocresol. In a sensitization experiment in human volunteers, there were no positive results in any of the 283 people tested.

14. Chlorocresol is very widely used in human medicines intended for parenteral and topical use at a concentration of 0.1-0.2%. It is also used as an active ingredient in some vaporizing fluids, intended for the treatment of nasal congestion, at a concentration of 10%. It is considered to be less toxic to humans than phenol and serious adverse reactions are rare. The most frequently-reported adverse reaction was dermatitis from the use of creams and ointments. Cases of hypersensitivity have occasionally been observed following the administration of injections containing chlorocresol as a preservative.

15. No residues depletion studies were carried out to determine the concentration of chlorocresol in tissues of treated animals. However chlorocresol was rapidly metabolised and excreted and showed no potential to accumulate in tissues. Consequently consumers are not likely to be exposed to residues of toxicological or microbiological significance.

16. Phenolic compounds are normal constituents of animal and human tissues and are found in urine and faeces. Background levels of phenols arise from microbial metabolic activities. Cresols are formed on reductive degradation of soil humic acids and fungal phenolic polymers. Chlorinated phenols are produced in detectable quantities during the chlorination of drinking and waste waters - the residues result from a halogenation of endogenous phenols. Concentrations in the range of 0.2-0.7 µg/l of chlorocresol have been found in surface waters.

Conclusions and recommendation

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

- Chlorocresol is of low toxicity;
- Chlorocresol is rapidly metabolised and excreted with no potential to accumulate in tissues;
- Chlorocresol had been safely used in human medicine for many years.

The Committee considers that there is no need to establish an MRL for chlorocresol and recommends its 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
Chlorocresol	All food producing species	