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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

8-HYDROXYQUINOLINE

SUMMARY REPORT

1. 8-Hydroxyquinoline (CAS 148-24-3; synonyms: quinoline-8-ol, 8-hydroxy benzopyridine, 8-quinolinol, oxyquinol, oxine), a heterocyclic phenol, is a metal chelator with antimicrobial and antifungal activity. The substance exists as a free lipophilic base or in form of water soluble salts (e.g. as sulphate). This MRL application is limited to the use of 8-hydroxyquinoline sulphate for topical treatment of umbilical infections in newborn animals (cattle, sheep, goats, pigs and horses). The substance is used at a concentration of 0.1% in an ointment preparation. The dosage is 0.5 to 1 g of the product 2 times daily for 4 to 5 days. This corresponds to a maximum of 2 mg 8-hydroxyquinoline sulphate per animal per day. As the weight content of the base 8-hydroxyquinoline in 8-hydroxyquinoline sulphate is 71% the daily dose of the free 8-hydroxyquinoline base is about 1.4 mg/animal or 7 mg (cumulative dose) within 5 days.

   The compound is used in human medicine as skin disinfectant and in hair-shampoos at low concentrations of 0.03 to 0.3%. It is also used as a pesticide for grapevine graft disinfection.

2. 8-Hydroxyquinoline is a substance which readily forms stable metal chelates. Its bacteriostatic and fungistatic action is believed to be due to the chelation of essential trace minerals on the surface of bacteria and fungi. Connection to the phenolic properties of the substance or to the intrinsic toxicity of the metal chelates themselves is also discussed. Chelation of metals with 8-hydroxyquinoline is thought to facilitate the transport of the metals across biological membranes. Concurrent oral administration of nickel was reported to significantly increase nickel uptake in mice. Deposition of iron in many tissues of rats is a typical effect of administration of 8-hydroxyquinoline. 8-Hydroxyquinoline was reported to inhibit arachidonic acid-induced platelet aggregation *in vitro* and platelet-activating factor-induced platelet aggregation. No NOELs for pharmacological properties are known.

3. Pharmacokinetic information on 8-hydroxyquinoline was limited. No information on absorption, distribution, metabolism and excretion after oral or dermal administration was available for laboratory or target species. After intravenous administration to rats (15 mg/kg bw), 8-hydroxyquinoline was found to be metabolised forming sulphate and glucuronide conjugates, which were rapidly excreted via urine, (approximately 60% of the dose as the sulphate within 8 hours and approximately 23% and 9% of the dose as the glucuronide via urine and bile, respectively). Reabsorption from the intestinal tract of the biliary excreted glucuronide conjugate was noted. No information on tissue distribution of the parent compound and/or its metabolites was available. No figures for the elimination half-life value(s) of the parent compound in blood were calculated.

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4. Oral LD_{50} values of 1200 to 2300 mg/kg bw were reported in rats for 8-hydroxyquinoline and 800 mg/kg bw for the sulphate. For guinea pigs, an LD_{20} of 1205 mg/kg bw was stated. In mice the reported values for the oral LD_{50} were 220 to 280 mg/kg bw. The LD_{50} after intraperitoneal and subcutaneous injection were given as 48 mg/kg bw and 83 mg/kg bw, respectively.

   Other authors reported both oral and subcutaneous LD_{50} values in mice to be 7.5 mg/animal and the topical LD_{50} value for mice to be 6 mg/animal. Oral LD_{50} values of 2520 to 3180 mg/kg bw and 1200 to 2520 mg/kg bw for male and female beagle dogs, respectively, were reported for 8-hydroxyquinoline sulphate. Adequate data on acute toxicity were rare: some symptoms of acute intoxication with 8-hydroxyquinoline were described in mice during the determination of the intraperitoneal LD_{50}. Doses of 8-hydroxyquinoline which kill the test animals within 5 to 10 minutes were reported to cause confusion, respiratory difficulty, occasional hind leg paralysis and, terminally, violent convulsions. Doses leading to delayed death (later than 6 hours post administration) result in anorexia, malaise, slow protective reflex action and general indifference to optical and acoustical stimuli. In acute toxicity studies in dogs single intravenous doses of 10 mg/kg bw and above induced significant central nervous system toxicity, presenting as anxiety, aggression, or convulsions.

5. The only information with respect to subchronic toxicity of 8-hydroxyquinoline originates from dose range finding investigations for carcinogenicity studies in rats and mice (5 to 15 animals/sex/dose) over 15 days (up to doses of 50 000 mg/kg feed) and 13 weeks (up to doses of 12 000 mg/kg feed in rats and 6 000 mg/kg feed in mice). From these studies only survival figures, terminal bodyweights and gross necropsy results were reported. Doses higher than or equal to 3 000 mg/kg feed led to impalatability of the food, inducing decreased food consumption and bodyweights. In the 13-week studies survival and overt organ pathology were not affected. No information on haematological, clinic-chemical parameters and histopathology was available. Levels of 50 000 mg/kg feed and 25 000 mg/kg feed were not tolerated by rats and mice, respectively, leading to death in several rats and all mice.

   The copper chelate of 8-hydroxyquinoline was investigated in oral 13-week repeated dose toxicity studies in rats and mice. At doses of 100 mg/kg bw and above liver and lymph tissue changes as well as haematopoietic effects like anemia and reduced leukocyte counts were noted. In dogs, oral administration of copper 8-hydroxyquinoline for 104 weeks in feed at doses greater than 6 mg/kg bw lead to anaemia, liver and kidney lesions as well as gastric intolerance. The NOELs for the copper chelate in the rodent species and dogs were determined as 30 mg/kg bw and 6 mg/kg bw, respectively.

6. No data on the tolerance of 8-hydroxyquinoline in the target animals are available.

7. Data on reproductive toxicity, embryotoxicity and teratogenicity of 8-hydroxyquinoline were not available. However, results of studies on the respective copper chelate did not reveal reproductive toxicity in a 2-generation study in rats at dietary levels of up to 500 mg/kg feed and no teratogenic or embryotoxic activity up to maternotoxic doses of 800 mg/kg bw and 30 mg/kg bw in rats and rabbits, respectively.

8. 8-Hydroxyquinoline caused mutations in the *Salmonella*/microsome assay with metabolic activation at doses of 20 to 40 µg/plate, in strains TA98 and TA100 but not in strains TA1535 and TA1537. In other studies, positive results were found at higher doses of about 100 µg/plate. Also, in *in vitro* mammalian cell systems, 8-hydroxyquinoline has shown dose-related gene mutation activity at concentrations of 0.4 to 3.2 µg/ml in a mouse lymphoma forward mutation assay and clastogenic effects in human lymphocytes at concentrations of 2.6 to 5.3 µg 8-hydroxyquinoline sulphate/ml.

Chromosomal aberrations in mouse bone marrow cells were observed after intraperitoneal treatment with 40 mg/kg bw. In an *in vivo* micronucleus test in mice the number of micronucleated monochromatic erythrocytes was dose-dependently increased 24, 48, and 72 hours after a single intraperitoneal treatment with 8-hydroxyquinoline at doses of 25, 50 or 100 mg/kg bw and the number of micronucleated polychromatic erythrocytes were slightly but significantly increased 24 hours after 100 mg/kg bw and 48 and 72 hours after 25 and 50 mg/kg bw, respectively. On the other hand the compound showed negative results in *in vitro* unscheduled DNA synthesis (UDS) tests in rat hepatocytes and in a second micronucleus test in mouse bone marrow *in vivo* after intraperitoneal doses of up to 70 to 100 mg/kg bw.

On the basis of available information definite conclusions regarding genotoxic properties of 8-hydroxyquinoline could not be drawn. It may be retained however, that the compound was mutagenic in bacterial test systems, exerted positive effects in mammalian *in vitro* gene and chromosomal mutagenicity tests and variable effects in *in vivo* chromosomal mutagenicity tests in mammals.

9. As regards carcinogenicity of 8-hydroxyquinoline some positive results of borderline significance were reported in the open literature for different routes of administration (oral, dermal, intravaginal, rectal administration and after instillation into the urinary bladder). The studies were of limited value due to for example small animal numbers and lack of concurrent controls.

   Adequate long-term dietary studies at concentrations of 1 500 or 3 000 mg 8-hydroxyquinoline/kg feed in F344/N rats (50/sex/dose) and B6C3F1 mice (50/sex/dose) for 111 weeks (rats) or 110 to 113 weeks (mice) failed to elicit significant increases of tumours. A trend for increased numbers of lung tumours in both species was not considered compound related. In rats the low dietary concentrations corresponded to 73 and 89 mg/kg bw for males and females, respectively, and the high dietary concentrations corresponded to 143 and 166 mg/kg bw for males and females, respectively. In mice the low dietary concentrations corresponded to 217 and 349 mg/kg bw for males and females, respectively, and the high dietary concentrations corresponded to 396 and 619 mg/kg bw for males and females, respectively. Bodyweights were reduced, possibly caused by decreased food consumption due to low palatability of medicated feed. No negative influence on survival figures was noted in rats or mice. The data from oral dietary carcinogenicity studies in rats and mice do not suggest a carcinogenic activity of 8-hydroxyquinoline in rodents.

   In a 78-week dietary carcinogenicity study in rats in which animals were treated with 8 000 mg/kg feed (about 400 mg/kg bw) no significant increase in tumour incidence was noted. Liver weights were slightly increased and iron deposition was observed in several tissues (spleen, liver, heart, kidneys etc.). This effect was noticed in test animals after 4 weeks on treatment already.

10. Studies on other effects of 8-hydroxyquinoline are lacking. Partly irreversible neurotoxic effects, the so-called subacute myelo-optic neuropathy, have been attributed to halogenated hydroxyquinoline derivatives after short-termed high dose or long-termed low dose oral administration to diarrhoic human patients beginning at oral doses of higher 10 mg/kg bw and above. Primates are considered more sensitive than other mammals but valid animal models are not available at present. No information or adequate epidemiological data are available to assess neurotoxic properties of orally administered 8-hydroxyquinoline and/or its metabolites in humans.

11. No adequate information on the antibacterial activity and MIC values of 8-hydroxyquinoline is available and no conclusion on microbiological ADI in respect to the human gut flora can be made for the substance.

12. Dermal administration of 8-hydroxyquinoline was reported to induce allergic responses in human patients.

13. No information on residues was submitted.

14. 8-Hydroxyquinoline has been evaluated by the International Agency for Research on Cancer (IARC) in 1977 and 1987 and by the US Cosmetic Ingredient Review (CIR) Expert Panel, in 1992. As concerns the IARC evaluations inadequate evidence for animal carcinogenicity was stated and the CIR Expert Panel in 1992 noted, that the available negative oral carcinogenic assays were not sufficient to conclude on the safety of use of 8-hydroxyquinoline in humans exposed to this compound in cosmetic skin products.

Conclusions and recommendation

In spite of the fact that an ADI for 8-hydroxyquinoline could not be established, nevertheless, 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:

- 8-hydroxyquinoline is intended for topical use in new-born animals only,
- 8-hydroxyquinoline is used in individual animals only and treatment is not in connection with the possible time point of slaughter,
- any absorbed fraction of this dose is expected to be rapidly metabolised and excreted,

the Committee concludes that there is no need to establish MRLs for 8-hydroxyquinoline and recommends its inclusion in Annex II of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
8-Hydroxyquinoline	All mammalian food producing species	For topical use in newborn animals only