



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

HYDROXYETHYLSALICYLATE

SUMMARY REPORT

1. Hydroxyethylsalicylate (2-Hydroxybenzoic acid 2-hydroxyethyl ester; CAS Number 87-28-5) is a non-steroidal anti-inflammatory drug (NSAID) belonging to the group of the salicylates. Other salicylates have been previously assessed by the Committee for Veterinary Medicinal Products.

Salicylic acid, is the basic substance of the salicylates which are non-steroidal anti-inflammatory drugs (NSAIDs). Salicylic acid (2-hydroxybenzoic acid; CAS Number 69-72-7) and methyl salicylate (ester) (methyl 2-hydroxybenzoate, wintergreen oil; CAS Number 119-36-8) are the main therapeutically used substances of this group. Because of their irritating effect on the gastrointestinal mucosa, salicylic acid and methyl salicylate are nearly exclusively used as external rubefacient substances for treatment of neuralgia, myalgia, arthralgia and other pains arising from integumental structures, thus also certain rheumatic diseases. As methyl salicylate can be absorbed through the skin it is used in counterirritant ointments and analgesic balms for painful muscles or joints.

Salicylic acid and its sodium and aluminium salts and methyl salicylate are used in cattle, horses, sheep, goats and poultry. They are used topically in creams, ointments or solutions for the cleaning of wounds of the skin and the teat. The recommended dose is 2 to 400 µg/kg bw/day. The recommended doses of topical salicylate are 100 times lower than the corresponding doses of acetylsalicylic acid given parenterally or orally in pigs, cattle and chickens (usually at a dose of 50 to 100 mg/kg bw orally or by injection).

Methyl salicylate is used topically in emulsion in the treatment of muscular and articular pain. The recommended dose is 600 µg/kg bw twice a day. The duration of treatment is usually less than one week.

Salicylic acid, sodium salicylate, aluminium salicylate, basic, and methyl salicylate are currently included into Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Salicylic acid	All food producing species except fish	For topical use only
Sodium salicylate	All food producing species except fish	For topical use only
Aluminium salicylate, basic	All food producing species except fish	For topical use only
Methyl salicylate	All food producing species except fish	For topical use only

An application has now been submitted to include hydroxyethylsalicylate for topical use in Annex II of Council Regulation (EEC) No. 2377/90.

2. Hydroxyethylsalicylate is closely related to methylsalicylate. The difference between the two molecules is based on substitution of the methyl moiety by an hydroxyethyl moiety in hydroxyethylsalicylate. Hydroxyethylsalicylate is intended for the treatment of muscular and articular pain in horses. The highest recommended therapeutic dose would be 5 mg hydroxyethylsalicylate/kg bw/day or 3.8 mg salicylic acid equivalent/kg bw/day (on a molecular weight basis: 138.12/182.18), divided into three daily doses, for 3 to 5 consecutive days. The recommended doses of topical hydroxyethylsalicylate would be 10 to 20 times lower than the corresponding doses of acetylsalicylic acid given parenterally or orally in pigs, cattle and chickens.

In human medicine hydroxyethylsalicylate is used in topical rubefacient preparations at concentrations of 5% to 15% for the relief of muscular and rheumatic pain.

Hydroxyethylsalicylate is composed of salicylic acid and ethylene glycol. The pharmacological activity of hydroxyethylsalicylate is attributable to the salicylic acid moiety. The mechanism of action of the salicylates is based on the inhibition of the cyclo-oxygenase enzyme that intervenes in the synthesis of prostanoids from arachidonic acid, just as all salicylic acid derivatives. They also inhibit the release of PGF_{2a} and PGE_2 from thrombin-stimulated platelets as well as the synthesis of thromboxanes and favour the production of prostacyclin PGI_2 . No pharmacological NOEL for salicylates was established. However, the pharmacological profile of salicylic acid is comparable to that of acetylsalicylic acid for which a pharmacological ADI of 0.0083 mg/kg bw (0.5 mg/person) was established. Ethylene glycol has no known pharmacological activity at the dose at which it is topically administered (1.66 mg/kg daily in horses) and has no therapeutic application in human or veterinary medicine.

3. After application of 5 g of an ointment or a gel containing 625 mg hydroxyethylsalicylate (corresponding to 473,9 mg salicylic acid) upon a skin area of 100 cm² of 12 normal volunteers, means of 26,7% (ointment) and 48% (gel) of the applied salicylate dose were absorbed within 24 hours and excreted in urine within 48 hours.

Twenty-eight healthy male volunteers were treated with 0.5 mg of methylsalicylate or hydroxyethylsalicylate onto the skin after dilution in acetone or methanol for 4 hours. The percentages of absorption were 87.8% for methylsalicylate and 92.9% for hydroxyethylsalicylate. These experimental conditions do not reflect actual clinical conditions but indicate that the absorption rate of methylsalicylate and hydroxyethylsalicylate are of the same order.

Hydroxyethylsalicylate is hydrolysed into salicylic acid and ethylene glycol.

Salicylic acid is partly excreted as such and partly metabolised to the glycine conjugate salicyluric acid and to the glucuronic acid conjugates salicyl-phenolic-glucuronide and salicyl-aryl-glucuronide and the oxidation product gentisic acid.

Ethylene glycol is metabolised into glycolic acid and oxalate via the alcohol dehydrogenase pathway.

No pharmacokinetic data were provided following topical application of hydroxyethylsalicylate in target animals.

4. No toxicological data on hydroxyethylsalicylate have been submitted. Reference was made to the previous evaluation of salicylic acid salts and esters. Since hydroxyethylsalicylate is hydrolysed into salicylic acid and ethylene glycol, the toxicity of both components has been considered.

A pharmacological ADI of 0.0083 mg/kg bw (i.e. 0.5 mg/person) was established for acetylsalicylic acid.

An ADI for methylsalicylic acid was set at 0 to 0.5 mg/kg bw by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1967 based on a 2-year feeding study in dogs and using a safety factor of 100. The same ADI based on a 2-year rat study in 1963 was adopted by the Council of Europe Committee of Experts on Flavouring Substances.

Only literature data on ethylene glycol toxicity have been provided.

Ethylene glycol has several industrial applications such as automotive radiator antifreeze and use as a coolant or solvent. Most ethylene glycol exposures result from the accidental ingestion of antifreeze.

Ethylene glycol ingestion in humans can initially result in inebriation. Any symptomatic patient with serum ethylene glycol higher than 100 mg/l 2 hours post-exposure should be admitted to hospital for treatment. The toxic plasma level is of 200 mg/l and fatal level is 850 mg/l.

Acute ethylene glycol toxicity is observed in humans after oral absorption of a dose of about 1000 mg/kg bw. Toxic effects arising from ingestion of ethylene glycol result from its major metabolites: aldehydes, glycolate, lactate, and oxalate. Clinical features may be divided into three stages depending on the time elapsed since ingestion. In the first 12 hours, the patient may show signs of drunkenness and experience nausea and vomiting. Convulsions and neurological defects may occur. From 12 to 24 hours, there may be tachycardia, mild hypertension, pulmonary oedema and heart failure. Between 24 and 72 hours, patients with severe ethylene glycol poisoning may experience flank pain and renal involvement with associated decreased plasma concentrations of calcium and bicarbonate, metabolic acidosis, deposition of oxalate in tissues and kidney tubules, proteinuria, oxaluria, haematuria, and renal failure. There may be respiratory failure, cardiovascular collapse, and sometimes coma and death. The lower fatal dose is reported to be about 100 ml (1000 mg/kg bw).

Lethal doses of ethylene glycol have been determined in several animal species after oral administration: 6140 mg/kg bw in rats, 14600 mg/kg bw in mice, 8200 mg/kg bw in guinea-pigs, 6600 and 8810 mg/kg bw in dogs, 2000 to 10000 mg/kg bw in cows and approximately 4500 mg/kg bw in poultry.

5. Daily oral administration of ethylene glycol in monkeys by gavage for 3 years at doses up to 150 mg/kg bw failed to induce toxicity.
6. Dams were administered ethylene glycol on gestation days 6-15: rats were given 0, 150, 500, 1000 or 2500 mg/kg bw/day; mice were given 0, 50, 150, 500 or 1500 mg/kg bw per day. NOELs for developmental toxicity were 500 mg/kg bw for rats and 150 mg/kg bw for mice. Higher doses induced several malformations in fetuses such as hydroencephaly, umbilical hernia, poor ossification and reduced body weight.

Artificially inseminated New Zealand White rabbits were administered ethylene glycol orally on gestation days 6-19. The highest tested dose of 2000 mg/kg bw per day failed to induce any malformation in fetuses but induced renal pathology, mortality, early deliveries and abortion in the dams.

Pregnant mice were given ethylene glycol on gestation days 6-15 by occluded cutaneous application 6 hours per day at doses of 0, 404, 1677 and 3549 mg/kg bw per day. No significant maternal or developmental toxicity was observed.

7. No information on ethylene glycol mutagenicity was provided.
8. No evidence of ethylene glycol carcinogenic activity was observed in mice administered daily doses up to 6000 mg/kg bw in feed for two years.
9. Hydroxyethylsalicylate is well tolerated in humans. Two hundred and fifty $\mu\text{g}/\text{cm}^2$ was not irritating to the skin of healthy human volunteers.

In horses, the application of a therapeutic dose of hydroxyethylsalicylate failed to induce any local or systemic adverse effects after 8 days of treatment. In particular, all blood parameters relating to coagulation remained unchanged: platelet counts, thromboelastogram, partial thromboplastin time, thromboplastin time, thrombin time, antithrombin III concentration.

10. No residue depletion data were provided. However, the amount of salicylic acid residues likely to be present in edible tissues following topical application of hydroxyethylsalicylate was considered negligible compared to the oral and parenteral administration of acetylsalicylic acid. For acetylsalicylic acid, which like hydroxyethylsalicylate is hydrolysed into salicylic acid, it was considered that the residues following oral and parenteral administration do not represent a risk for the consumer. No conclusion could be drawn regarding possible residues of ethylene glycol.

11. No information on residue depletion of ethylene glycol has been provided since it was considered that ethylene glycol is a not pharmacologically active substance at the dose administered.

Conclusions and recommendation

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

- hydroxyethylsalicylate is used in a small number of individual animals, for infrequent or non-regular treatments,
- the animals are unlikely to be sent for slaughter during or immediately after treatment,
- after topical application the amount of residues likely to be ingested by consumers is considered negligible;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for hydroxyethylsalicylate 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
Hydroxyethylsalicylate	All food producing species except fish	For topical use only