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

EMEA/MRL/696/99-FINAL
November 1999

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

SALICYLIC ACID, SODIUM SALICYLATE, ALUMINIUM SALICYLATE, BASIC, AND METHYL SALICYLATE

SUMMARY REPORT

1. 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 gastro-intestinal 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 intertegumental 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 salt and methyl salicylate are used in cattle, horses, sheep, goats and poultry. It is used topically in cream, ointments or solution for the cleaning of wounds of the skin and the teat. The recommended dose is 2 to 400 µg/kg bw/day. 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. 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).

   In human medicine salicylic acid is used by oral route and topical application.

   Methyl salicylate is also widely used as a flavouring agent in numerous foods and beverages.

2. 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. There is a reasonably good rank-order correlation between the potency of cyclo-oxygenase inhibition and their anti-inflammatory activity. This effect depends only on the drug reaching the enzyme. No pharmacological NOEL for salicylates can be established due to the insufficient data provided. The pharmacological profile is comparable to acetylsalicylic acid. In humans, the lowest therapeutic oral dose of acetylsalicylic acid is 50 mg/person.

3. In rats, after oral administration of 500 mg methylsalicylic acid/kg bw, the drug was nearly completely hydrolysed to salicylate within 1 hour and at this time the concentrations of free salicylates in plasma and brain were 278 and 42 µg/ml. These levels are similar to those observed after the administration of acetylsalicylic acid. A similar pattern of hydrolysis was also observed in dogs.

   The liver is the main site of methyl salicylate hydrolysis in rats, rabbits, dogs and monkeys.

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In dogs 0.2 to 0.5% of an oral dose and 14% of an intramuscular dose are excreted as unchanged methylsalicylic acid in the urine. Rabbits excrete methylsalicylic acid mainly as glucuronate (12 to 55%) but also as sulphate (10%) conjugate.

Methyl salicylate is extensively metabolised to salicylic acid in dermal and subcutaneus tissues following topical administration.

In humans approximately 12 to 20% of topically applied methylsalicylic acid is systemically absorbed within 10 hours of application. When methylsalicylic acid was given orally to 6 healthy adults, about 21% of unhydrolysed ester was present in plasma after 90 minutes. In a case of an accidental oral intake of wintergreen oil 21% was present in the circulation after 1.5 hours.

No pharmacokinetic data were provided following topical application in animals.

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.

No data on oral bioavailability have been provided.

4. Only documentation related to acetylsalicylate was provided. The following information was extracted from summary data of toxicological studies available.

   The acute oral toxicity of methylsalicylic acid has been investigated in several animal species. Oral LD_{50} values of 1110 mg/kg bw in mice, 887 and 1250 mg/kg bw in rats, 2100 mg/kg bw in dogs, 1300 and 2800 mg/kg bw in rabbits have been reported. Administration of 600 to 4700 mg/kg bw of methylsalicylic acid to dogs produced nausea, vomiting, intense hyperpnoea, excitation of the nervous system, diarrhoea and a hypermetabolic state as a result of uncoupling of oxidative phosphorylation.

5. In a sub-acute 13-day toxicity study in rats, methylsalicylic acid induced alterations of microbodies in the hepatocytes when given at a dietary level of 0.1% (approximately 50 mg/kg bw). Rats given methylsalicylic acid in their diet for up to 10 weeks at a dose of approximately 1000 mg/kg bw showed reduced growth and reduced chondroclastic and osteoclastic activity. Similar findings were not observed in animals receiving approximately 450 mg/kg bw or less. In a 17-week dietary study, rats were fed 0, 0.1 and 1% of methylsalicylic acid in their diet, corresponding to approximately 0, 50 and 500 mg/kg bw. A significant reduction in growth rate was observed at dietary levels corresponding at approximately 500 mg/kg bw. As only summary information was available no NOEL could be established.

   In dogs methylsalicylic acid given at doses of 0, 50, 150, 250, 500 and 800 mg/kg bw for up to 10 weeks, induced weight loss, liver fatty degeneration and death at doses of 500 mg/kg bw or higher. No adverse effects were noted after doses as high as 250 mg/kg bw. As only summary information was available no NOEL could be established.

   When methylsalicylic acid was administered topically to rabbits for 90 days (0.5, 1, 2 and 4 ml/kg bw/day), early deaths and kidney damage were observed at all dose tested. As only summary information was available no NOEL could be established.

6. Chronic toxicity studies were performed in rats and dogs.

   In a 2-year toxicity study in rat, methylsalicylic acid was given at dietary concentrations of 0, 0.1, 0.5, 1 and 2%, corresponding to doses of 0, 50, 250, 500 and 1000 mg/kg bw. At the hight dose level, the mortality was 100% (within week 49 of the study). Signs of toxicity such as reduced growth rate, increase in relative weight of testes, heart and kidneys in animals treated with 500 mg/kg bw and gross pituitary lesions in animals treated with 250 mg/kg bw were also observed. Excess cancellous bone formation was observed at doses of 250 mg/kg bw or more. In another 2-year feeding study no adverse effects were observed up to a level of 0.21% of methylsalicylic acid in the diet (approximately 100 mg/kg bw) which was the highest dose tested. As only summary information was available no NOEL could be established.

In a 2-year toxicity study in dogs methylsalicylic acid was given at 0, 50, 150 and 350 mg/kg bw. Growth retardation, liver enlargment with enlarged hepatocytes were observed at doses of 150 mg/kg bw or more. As only summary information was available no NOEL could be established.

7. Reproduction-toxicity and teratogenicity studies were carried out in rats and hamsters.

   In rats subcutaneous administration of 0.1 ml methylsalicylic acid on day 10 or day 11 of gestation caused a higher incidence of foetal resorptions and malformations.

   In hamsters methylsalicylic acid was also found to provoke teratogenic effects at both high oral doses (1750 mg/kg bw) and high topical doses (1750 to 14000 mg/kg bw). As only summary information was available no NOEL could be established.

8. In two 3-generation studies in rats at 25, 50, 150 and 250 mg/kg bw no adverse effects were observed at 50 mg/kg bw. The salicylate but not its metabolites was found to be primarily or solely responsible for the teratogenic effects in rats.

9. No studies on genotoxicity were submitted. Acetylsalicylic acid, which like methylsalicylic acid, is hydrolysed to salicylic acid, was considered not genotoxic. Therefore, salicylic acid and methylsalicylic acid can be considered as devoid of genotoxicity.

10. No studies on carcinogenicity were provided.

11. Salicylates depress prothrombin formation in the liver. Methylsalicylic acid at 8% in petrolatum jelly in 27 human volunteers did not provoke sensitisation reactions.

    The adverse effects of methyl salicylate ingestion are more severe with a rapid onset because of its liquid concentrated form and lipid solubility. It is readily absorbed from the gastro-intestinal tract and most of it is rapidly hydrolysed to free salicylic acid. The symptoms, which may appear after 2 hours, are similar to those of salicylate poisoning in general although methyl salicylate is expected to be more toxic because of its lipid solubility. Toxicological signs in cases of massive ingestion of methyl salicylate would include cardiovascular, central nervous system, dermatological, endocrine, gastro-intestinal, haematological, hepatic, neuromuscular, ocular, otic, renal, and respiratory signs. The lowest doses reported to be lethal are 4.7 g in children and 7.1 g in adults.

12. Methylsalicylic acid is also widely used as a natural flavouring substance in foods and beverages such as baked goods, gelatin and puddings, frozen dairy dessert, confectionery, chewing gum, soft drinks, spirit and liqueurs. The ordinary consumption of one of the food-categories involved amount to a daily intake of 0.01 to 0.29 mg/kg bw. Extreme consumption of one of the food-categories would lead to a daily intake of 0.04 to 1.59 mg/kg bw while extreme consumption of all the foods and beverages together could give a daily intake of 2.43 mg/kg bw.

13. 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.

14. No pharmacological and toxicological ADI could be established for salicylic acid and methylsalicylic acid.

15. No residue depletion data were provided. However, the amount of salicylic acid and methy salicylate residues likely to be present in edible tissues following topical application was considered negligible compared to the oral and parenteral administration of acetylsalicylic acid in cattle and pigs.

16. An HPLC analytical method with spectrofluorimetric detection described in the ISO 78/2 format was proposed for the determination residues of salicylic acid in pigs and cattle tissues. The limit of quantification was 50 µg/kg for fat, liver and kidney and 100 µg/kg for muscle. No method for the determination of residues in milk was provided.

17. For acetylsalicylic acid, which like methylsalicylic acid is hydrolysed into salicylic acid, it was considered that the residues following oral and parenteral administration do not represent a risk for the consumer.

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:

- salicylic acid and methy salicylate are used topically 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,
- methylsalicylic acid is widely used as a natural flavouring substance in foods and beverages,
- 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 salicylic acid, sodium salicylate, aluminium salicylate, basic, and methyl salicylate and recommends their 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
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