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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MENTHAE PIPERITAE AETHEROLEUM

SUMMARY REPORT

1. *Menthae piperitae aetheroleum* (synonym: peppermint oil) is the volatile oil obtained by steam distillation from leaves and twigs of *Mentha x piperita* L. It contains menthol (35 to 45%), menthone (15 to 20%), 1,8-cineole (6 to 8%), methylacetate (3 to 5%), neomenthol (2.5 to 3.5%), isomenthone (2 to 3%), menthofuran (2 to 7%), limonene (2 to 3%), pulegone (0.5 to 1.5%), a-pinene (1 to 3.5%), ß-pinene (1 to 2%), *trans*-sabinene hydrate (1.0%), isopulegol (0.5 to 0.8%), ß-caryophyllene (0.5 to 1.5%), germacrene D (1 to 2%) and ß-bourbonene (0.5%).

2. *Menthae piperitae aetheroleum* is contained at a concentration of 0.018% in one veterinary medicinal product which also contains 5 other active ingredients. It is used orally to treat bronchitis, laryngitis, catarrh of the upper respiratory tract, bronchopneumonia, pleurisy and pneumonia in horses, cattle, sheep, goats and pigs. The dose of 50 ml is given twice daily. The daily dose of 100 ml corresponds to about 16 mg of *Menthae piperitae aetheroleum*.

   Menthae piperitae aetheroleum is also used in human medicine for the symptomatic treatment of digestive disorders (e.g. flatulence, irritable bowel syndrome) at oral doses of 0.2 to 0.4 ml three times daily. For the symptomatic treatment of coughs and colds *Menthae piperitae aetheroleum* is used by inhalation (3 to 4 drops added to hot water) in lozenges containing 2 to 10 mg. Topical administration of *Menthae piperitae aetheroleum* is used for symptomatic relief of coughs and colds, rheumatic complaints, pruritus, urticaria at concentrations of 0.1 to 1.0% w/w and of pain in irritable skin conditions at concentrations of 1.25 to 16% w/w.

   Peppermint leaves, which contain 0.5 to 4% v/w of volatile oil, are widely consumed in the form of tea. *Menthae piperitae aetheroleum* is also used as a flavouring agent in foodstuffs for human consumption (sweets, chewing gums, baked goods, alcoholic beverages).

3. *Menthae piperitae aetheroleum* has antimicrobial, choleretic and spasmolytic effect.

4. Within 4 hours 34.5% of a human oral dose of *Menthae piperitae aetheroleum* (0.4 ml) in a slow release formulation was excreted in the urine as glucuronide. In rats menthol is excreted in the urine as a glucuronide and in the bile as sulphate.

5. Acute toxic effects were observed in rats and mice at oral doses of 3 to 5 g/kg bw. The oral LD_{50} is about 4 g/kg bw for rats and mice.

6. The following summary information on repeated oral dose toxicity of *Menthae piperitae aetheroleum* was available. No adverse effects on blood and clinical parameters as well as on body weight were observed in rats after daily oral doses of 0, 10, 40, or 100 mg/kg bw for 4 weeks. The two high doses caused histological changes in the brain. Based on this investigation the highest safe dose for rats was estimated to be 10 mg/kg bw/day. In a 90-day study in rats at the same dose levels, the highest dose of 100 mg/kg bw caused cyst-like spaces in the white matter of the cerebellum and, in male rats only, nephropathy. No such changes were observed at 40 mg/kg bw.

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These findings are contradicted by other investigators who found no changes in rats given 20, 150 or 500 mg/kg bw/day for 5 weeks or dogs given 25 or 125 mg/kg bw.

The doses of *Menthae piperitae aetheroleum* without obvious toxic effect in the rat studies (10 and 40 mg/kg bw) are higher than the effective single oral dose in human of 0.2 ml, corresponding to approximately 2.5 mg/kg bw.

The following results are reported for the some of the constituents of *Menthae piperitae aetheroleum.* In rats receiving menthol by gavage at 0, 200, 400 and 800 mg/kg bw for 28 days, significant increase of absolute and relative liver weights and vacuolisation of hepatocytes was observed at all dose levels. Rats received pulegone by gavage for 28 days at doses of 0, 20, 80 and 160 mg/kg bw. Atonia, decreased blood creatinine content, lower terminal bodyweight and histopathological changes in liver and white matter of the cerebellum were observed. The NOEL for pulegone was 20 mg/kg bw. Menthol caused no adverse effects on the brain. Menthone and racemic menthone (0, 200, 400, 800 mg/kg bw/day) caused a dose dependent decrease of creatinine, an increased activity of alkaline phosphatase and bilirubin. Also the weight of the liver and the spleen increased. No NOEL was observed in this study.

7. No information on the effect on reproduction and on the teratogenicity of *Menthae piperitae aetheroleum* was provided.

8. *Menthae piperitae aetheroleum*, menthol and pulegone are not mutagenic in the Ames test. Menthone had some mutagenic effect in this test system.

9. No information on the carcinogenicity of *Menthae piperitae aetheroleum* was provided.

10. *Menthae piperitae aetheroleum* has only weak sensitising effect. Menthol can cause allergic reactions.

11. An adverse effect, i.e. heartburn, is occasionally observed in humans after ingestion of non-enteric-coated preparations of *Menthae piperitae aetheroleum*. Inhalation of menthol can cause apnoea and laryngoconstriction in susceptible persons, and in overdose cause reversible effects such as nausea, anorexia, cardiac problems and ataxia and other CNS-problems, but these effects have only rarely been associated with peppermint.

12. Menthol, the main constituent of *Menthae piperitae aetheroleum*, has already been included in Annex II to Council Regulation (EEC) No. 2377/90.

Conclusions and recommendation

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

- peppermint tea, which has a content of *Menthae piperitae aetheroleum* of 0.5 to 4%, is a normal component of the human diet,
- menthol, the main constituent of *Menthae piperitae aetheroleum* is already included in Annex II,
- *Menthae piperitae aetheroleum* is of low acute toxicity,
- the data indicate that *Menthae piperitae aetheroleum* is rapidly excreted,
- *Menthae piperitae aetheroleum* is used only for infrequent treatment of a small number of individual animals,
- animals are unlikely to be sent for slaughter during or immediately after treatment;

the Committee concludes that there is no need to establish an MRL for *Menthae piperitae aetheroleum* and recommends its inclusion in Annex II to Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Menthae piperitae aetheroleum	All food producing species	