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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

FOENICULI AETHEROLEUM

SUMMARY REPORT

1. *Foeniculi aetheroleum* is the oil obtained by steam distillation of the ripe fruits of *Foeniculum vulgare* Miller var. *vulgare*. This variety is also called bitter fennel. It contains *trans*-anethole (60 to 75%), (+)-fenchone (12 to 30%), estragole (2 to 7%), limonene, a-pinene, anisaldehyde, *p*-cymene, myrcene, sabinene (less than 0.5%) and other terpene derivatives in small amounts.

2. *Foeniculi aetheroleum* is contained in two veterinary medicinal products in combination with 9 and 4 other active principles, respectively. In one of these, the percentage of *Foeniculi aetheroleum* is 0.005%. This product is intended to be used as a nose-spray to facilitate breathing in new-born animals of all food producing species. The dose is 0.1 to 0.3 g of the product, depending on the size of the animal. This corresponds to a maximal single dose of 0.015 mg *Foeniculi aetheroleum*. The treatment may be repeated after 10 to 15 seconds. The second product contains 1% of *Foeniculi aetheroleum* and is prescribed for treatment of flatulence and disturbances of the stomach and gut. The dose ranges from a few drops to 15 ml, depending on body weight. The maximal dose corresponds to 150 mg of *Foeniculi aetheroleum*. Target species are cattle, horse, pigs, sheep and goats.

   Foeniculi aetheroleum is used in human medicine as a carminativum at a dose of 0.1 to 0.6 g/day.

   The fruit of *Foeniculum vulgare*, from which *Foeniculi aetheroleum* is obtained and which contains approximately 2 to 6% oil, is used extensively as a spice for seasoning of food. It is also used in medicinal tooth pastes and mouth washes and in cosmetic products (soaps, creams and lotions, perfumes at concentrations of 0.001 to 0.4%).

3. No pharmacokinetic data are available for *Foeniculi aetheroleum*, while the summary information provided contained some information on its main constituent. Following intravenous administration of 10 and 20 mg anethole/kg bw to rabbits only 0.025 and 0.5% of the dose remained after 150 minutes, respectively. Seventy-two hours following an oral dose of 50 mg/kg bw C^{14}-labelled anethole to rats, 85% of the radioactivity was excreted with the faeces, the urine and through the exhaled air. The same result was obtained with 50 mg labelled anethole/kg bw intravenous to mice. In man, anethole is excreted within 8 hours.

4. *Foeniculi aetheroleum* has antimicrobial activity, a spasmolytic effect on the ileum of rabbits, cats and rats and a secretolytic effect in rabbits. Fenchone has CNS stimulating effect.

5. The oral LD_{50} for rats is in the range of 3.1 to 4.5 g/kg bw. For *trans*-anethole the intraperitoneal LD_{50} values are 1.41 g/kg bw and 2.67 g/kg bw for mice and rats, respectively. The oral LD_{50} values for *trans*-anethole are 3.05 g/kg bw, 2.09 g/kg bw and 2.16 g/kg bw for mice, rats and rabbits, respectively. For fenchone the LD_{50} values for rats are 6.16 g/kg bw after oral and 0.1 g/kg bw after intraperitoneal administration. *Cis*-anethole is 10 to 20 times more toxic than *trans*-anethole but the content in the oil is very low (approximately 0.1%). Rabbits and dogs tolerate 3 g anethole per kg bw without any toxic manifestations. With respect to long-term toxicity, no data for the oil are available.

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6. No information on the repeated dose toxicity of *Foeniculi aetheroleum* was provided. For its main constituent the following summary information was available. Rats were fed anethole in the feed (10 g/kg feed) for 15 weeks. A one year feeding study showed that the NOEL for rats is 125 mg anethole/kg.

7. No information on reproduction and teratogenicity has been provided.

8. The summary information provided it was stated that *Foeniculi aetheroleum* and anethole are not mutagenic.

9. No studies have been performed on carcinogenicity of *Foeniculi aetheroleum*. Estragole has produced liver tumours in mice, but these are found to be related to the metabolite 1-hydroxyestragole only produced at high doses. In one study, where only summary information were available, it was found that the percentage of an administred dose of estragole eliminated as 1-hydroxyestragole glucoronide in human urine is much lower than found with the lowest doses examined in rats (figures not given).

10. No allergic manifestations are reported for *Foeniculi aetheroleum,* in a 4% preparation in paraffin, in a maximisation test in volunteers. Also no skin irritation was observed in 48 hour closed patch test in humans.

11. Acute or chronic poisoning of humans is not reported for *Foeniculi aetheroleum*.

12. Anethole and fenchone have "Generally Recognised As Safe" status in the USA. In 1991 the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established an ADI for *trans*-anethole of 0.6 mg/kg bw. A fenchone concentration of 5 mg/kg in food is permissible.

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:

- the fruit of *Foeniculum vulgare*, from which *Foeniculi aetheroleum* is obtained, is a normal component of the human diet,
- *trans*-anethole, the main constituent of *Foeniculi aetheroleum,* is rapidly excreted in man,
- *Foeniculi aetheroleum* is used only for occasional treatment of individual animals,
- animals are unlikely to be sent for slaughter immediately after treatment;

the Committee concludes that there is no need to establish an MRL for *Foeniculi aetheroleum* 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
Foeniculi aetheroleum	All food producing species	