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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CINNAMOMI CEYLANICI CORTEX

SUMMARY REPORT

1. *Cinnamomi ceylanici cortex*, cinnamon bark, is the stembark of *Cinnamomum verum* J.S. Presl. (synonym: *Cinnamomum zeylanicum* Blume), from which the outer cork layer has been removed. The main constituent of *Cinnamomi ceylanici cortex* is the volatile oil (0.5 to 2.5%), which mainly contains cinnamaldehyde (55 to 76%), eugenol (5 to 18%), and safrole (up to 2%). Seventy other components of the oil have been identified, among others cinnamic alcohol, cinnamic acid, o-methoxy-cinnamic aldehyde and cinnamyl acetate. The bark also contains tannins (up to 2%) and diterpenes such as cinnzeylanol and cinnzeylanin, which have insecticidal effect. Different sugars and a mucilage are also present.

2. An extract is used in veterinary medicine, but no further information has been obtained.

   In human medicine *Cinnamomi ceylanici cortex* is used as an appetite stimulant and as a carminative. Cinnamon bark is widely used as a spice. The volatile oil (*Cinnamomi ceylanici aetheroleum*) is used for flavouring human foodstuffs (chewing gum, non-alcoholic beverages, meat sausages) and as a fragrance in the cosmetic industry.

3. The essential oil (*Cinnamomi ceylanici aetheroleum*) is a cyclo-oxygenase inhibitor. The active compound is probably eugenol. The oil has antibacterial and antifungal activity, its constituent cinnamaldehyde being a fungotoxic. Cinnamaldehyde has a hypotensive effect in anaesthetised dogs and guinea pigs. Cinnamaldehyde is an inhibitor of stomach peristalsis in anaesthetised rats (5 to 20 mg/kg bw intravenously) and of the peristalsis in the gut of mice (250 mg/kg bw intraperitoneally). Cinnamaldehyde stimulates bile secretion in rats (500 mg/kg bw), has central nervous system-stimulating activity in rabbits (10 to 20 mg/kg bw intra-arterially) and inhibits motor activity in mice (250 to 1000 mg/kg bw oral doses). Cinnamaldehyde caused positive inotropic and chronotropic effects in isolated guinea pig heart preparations. Repeated application resulted in cardiac depression. Intravenous doses of 5 to 10 mg/kg bw and concentrations of 10 to 100 mg/l in organ preparations were used. Cinnamaldehyde (100 mg/l) has a papaverin-like spasmolytic effect on the isolated guinea-pig ileum and isolated mouse ileum.

   Cinnamomi ceylanici *aetheroleum* is also used in veterinary medicine. It has been previously assessed by the Committee for Veterinary Medicinal Products and included in Annex II of Council Regulation (EEC) No 2377/90 for all food producing species.

4. No information on pharmacokinetics of *Cinnamomi ceylanici cortex* was provided.

5. Ethanolic extracts of *Cinnamomi ceylanici cortex* were not toxic to mice at oral doses up to 3 g/kg bw (drug/extract ratio not given). In a 90-day experiment 100 mg/kg/day of the same extract, orally to mice caused no significant mortality compared to the control group. The treated animals did not change their weight while the weight gain in the control group was significant.

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Reduction in liver weight and significant fall in the haemoglobin level was recorded for the treated animals. In human high doses (no figures given) can cause convulsions, tachycardia, increased rate of breathing, increased peristalsis of the gut and increased production of sweat. Later on sleepiness and depression can set in. Toxical manifestations are due to the content of volatile oil. The oral LD_{50} for *Cinnamomi ceylanici aetheroleum* in rats is 4160 mg/kg bw. For cinnamaldehyde the oral LD_{50} in rats is 2220 mg/kg bw and in mice the intra peritoneal LD_{50} is 200 mg/kg bw. The dermal LD_{50} for the oil is 690 mg/kg bw. Other reports state the dermal LD_{50} as 0.69 mg/kg bw for the oil and 0.59 mg/kg bw for cinnamaldehyde. Rats tolerated oral doses of 70 mg cinnamaldehyde for 8 weeks without any symptoms of toxicity. Cinnamaldehyde added to the feed for rats at 1000 and 2500 mg/kg feed for 16 weeks caused no adverse effects. At 10 000 mg/kg feed slight swelling of the hepatic cells and slight hyperkeratosis of the squamous portion of the stomach were observed.

6. In 90-day studies on mice an oral dose for of 100 mg/day/kg bw of an ethanolic extract of *Cinnamomi ceylanici cortex* (crude drug/extract ratio not given) induced a significant increase in reproductive organ weights, sperm motility, sperm count and failed to illicit any spermatotoxic effect. In humans, cinnamon and preparations thereof are in older literature reported to have abortifacient effect. It must be taken into account that in old sources cinnamon (cassia) was confused with *Cassia fistulosa,* which contains anthraquinones.

7. Negative effects of the *Salmonella*-microsomal assay for mutagenicity of *Cinnamomi ceylanici cortex* were reported using *Salmonella typhimurium* TA 100 and TA 98.

   The following summary information on the mutagenicity of *Cinnamomi ceylanici aetheroleum* was available. Cinnamon oil is positive in the *Bacillus subtilis*-DNA repair test. In most experiments with the *Salmonella*-microsomal negative results have been obtained. For cinnamaldehyde both positive and negative results are reported. Cinnamon oil and cinnamaldehyde gave positive results in chromosomal aberration tests using Chinese hamster cell cultures and in *Drosophila* test systems. Negative results were reported with the *in vivo* micronucleus test in the mouse (125 to 500 mg/kg bw intraperitoneal). The results of the *in vitro* bacterial mutagenicity tests must be interpreted with caution as the concentrations used were within the dose range where antimicrobial effects of cinnamaldehyde or cinnamon oil have been demonstrated. Also for the *in vitro* tests with mammalian cell cultures it must be taken into account that cinnamon extracts and cinnamaldehyde have cytotoxic effects. Taking also into consideration the negative results of the *in vivo* micronucleus test, the positive *in vitro* findings can be considered of no concern.

8. No information on the carcinogenicity was provided. Compare, however, the above information on the lack of mutagenicity of the essential oil.

9. *Cinnamomi ceylanici cortex* is known to cause allergic reactions, due to the content of the volatile oil, particularly cinnamaldehyde which is the leading substance responsible for allergic reactions caused by cosmetics and perfumes. Allergic reactions have also been caused by toothpaste containing cinnamaldehyde.

10. A temporary ADI of 0.7 mg/kg bw was set for cinnamaldehyde by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1984 but was not extended further in 1992 because of incomplete toxicity data. The ADI of eugenol is up to 2.5 mg/kg. The bark (oil content up to 4%) is used for food flavouring and is listed by the Council of Europe (1973) as a natural source of food flavouring, category N2. This category indicates that cinnamon can be added to foodstuffs in small quantities, with a possible limitation of an active principle in the final product. The bark is listed as “Generally Recognised As Safe” in the United States of America.

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:

- *Cinnamomi ceylanici cortex* is a normal component of the human diet,
- *Cinnamomi ceylanici cortex* is used for occasional treatment of individual animals,
- animals are unlikely to be sent for slaughter immediately after treatment,
- *Cinnamomi ceylanici aetheroleum*, the main active constituent of *Cinnamomi ceylanici cortex* is already included in Annex II;

the Committee concludes that there is no need to establish an MRL for *Cinnamomi ceylanici cortex* and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 according to the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Cinnamomi ceylanici cortex standardised extracts and preparations thereof	All food producing species	