COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CAPSICI FRUCTUS ACER

SUMMARY REPORT

1.  *Capsici fructus acer*, cayenne pepper, is the dried ripe fruits of *Capsicum frutescens*.

   The constituents of *Capsici fructus acer* are: Capsaicinoids 0.3 to more than 1%, of which 63 to 77% is capsaicin, 20 to 32% dihydrocapsaicin, 1 to 8% nor-dihydrocapsaicin. The rest are other capsaicin derivatives in low concentrations. Other constituents are: fixed oil, volatile oil containing more than 125 components, carotenoids and ascorbic acid. The capsaicinoids are the main pharmacologically active compounds.

   *Capsici fructus acer* and its preparations are contained in two veterinary medicinal products. One preparation is a powder containing in total 14 active ingredients, with 10% (w/w) pulverised *Capsici fructus acer*, for oral administration to cows, horses, pigs, sheep and goats for the induction of heat and rut. The doses are 50 g/animal twice a day on two consecutive days for cattle and horses, and 10 to 20 g/animal twice a day on 3 to 4 consecutive days for sheep, goats and pigs.

   The other preparation is a solution containing five active herbal ingredients, one which is a tincture prepared with 60% isopropanol corresponding to 1 g *Capsici fructus acer*. This tincture constitutes 53.8% (w/w) of the finished product. The finished product is used for topical administration to all food producing species, particularly cows, horses, sheep and goats to treat strains and ruptures of muscles and tendons and against swollen joints. The dosages are not precisely stated, however dilutions between 1:1 and 1:5 are to be applied directly onto the skin, while dilutions between 1:5 and 1:10 are to be used for compresses.

   In humans a lotion or ointment containing extract of *Capsici fructus acer* or pure capsaicin is used topically for treatment of neuralgia, including rheumatic pains and unbroken chilblains. The concentration in semi-solid preparations corresponds to 0.02 to 0.05% capsaicinoids.

   *Capsici fructus acer* and capsaicin-containing fruits of other *Capsicum*-species have been frequently used in traditional medicine both topically and systemically for a number of diseases.

   In addition *Capsici fructus acer* is used as a spice in the human diet.

2.  Many pharmacological studies have been performed on crude, unsufficiently characterized, extracts of the fruit. These investigations are of limited value.

   The pharmacology of capsaicin has been thoroughly investigated. When applied to the skin typical inflammation symptoms appear, such as pain, feeling of heat and erythema. These are evoked by liberation of autacoids, also called tissue hormones (substance P, histamin, bradykinin and prostaglandins), at peripheral nerve endings and at the dorsal part of the spinal cord. This primary phase is short-lasting (a few hours) and is followed by a secondary phase where sensitivity to pain is reduced. This phase can last for hours up to several weeks. If capsaicin is applied to the same spot e.g. after 24 hours, the effects in the first phase are weaker.
Intragastric application in rats of 1 mg capsaicin/rat increased the ulcus index (89%) without effects on the amount, pH or acid content of the gastric juice. On the other hand, intraduodenal application caused an increase in the content of acid in the gastric juice but had no effect on the other parameters. In healthy individuals as well as in patients with duodenal ulcer, 0.4 g chili-powder, applied intragastrically 4 times within one hour, caused an increased production of acid and increased motility of the stomach.

In Guinea pigs which received 50 mg/kg bw subcutaneously of capsaicin no reaction in the hot plate test or to chemical irritation of the eye (zingeron) were observed even at three days following application. The reactions to pressure, cold and vibrations were, however, not affected.

3. About 85% of a dose of 13.6 mg/kg bw of a mixture of capsaicin and dihydrocapsaicin (85:15), applied to the standard diet of rats, was absorbed in 3 hours mostly in the jejunum. Both substances partly experienced a first-pass-effect. Dihydrocapsaicin and probably also capsaicin are partly hydrolysed in the wall of the gut.

Following intravenous administration of capsaicin (2 mg/kg bw) to rats the concentration of capsaicin in the brain and the spinal cord is 5 times higher and in the liver 3 times higher than in the blood. Ten minutes after the application the concentration in the blood and the liver is strongly reduced while capsaicin can still be detected in the brain and spinal cord.

Following subcutaneous administration to rats of 50 mg/kg bw of capsaicin the maximum concentration in the plasma is reached after 5 hours. The concentration of capsaicin in the brain, the spinal cord and the blood is about the same during the first 100 minutes following the administration. The concentration is higher in the kidneys than in the liver. After 17 hours no capsaicin can be detected in any of the organs.

Following subcutaneous administration of capsaicin or dihydrocapsaicin to rats in a dose of 50 mg/kg bw maximum concentration in the blood and the brain is obtained 6 hours after the injection. In the brain the concentration of dihydrocapsaicin is relatively higher than that of capsaicin while in the blood the opposite relationship is recorded.

Metabolites of capsaicin are mainly excreted as glucuronide conjugates in the urine.

It is not known whether the capsinoids are secreted with the breast milk. However, any appreciable amounts would cause rejection of the milk because of the sharp taste.

No information on the absorption of capsaicin through the skin and possible residues resulting from topical treatment of food-producing animals was provided. Absorption of capsaicin from the intestines is rapid (rat: 85% in 3 hours). Elimination is fast in the rat. Capsicin has a strong affinity to nerves but after 17 hours following subcutaneous administration of 50 mg/kg bw to rats, no capsaicin could be detected in any tissues.

4. For an extract (5:1) of the crude drug with a capsaicin content of 0.6% an oral LD$_{50}$-value of 155.6 mg/kg bw in male mice, corresponding to 4.67 mg/kg bw of capsaicin was observed.

The acute toxicity of capsaicin in animals shows great variations depending on the species, the age of the animals and the method of application. LD$_{50}$-values for intraperitoneal administration range from 1.1 mg/kg bw in Guinea pigs, 6.5 to 7.6 mg/kg bw in mice, 9.5 mg/kg bw in adult rats, 10.4 to 13.2 mg/kg bw in young rats to more than 50 mg/kg bw in rabbits and more than 120 mg/kg bw in hamsters. LD$_{50}$-values for intravenous administration are 0.6 mg/kg bw in mice and 1.6 to 4.3 mg/kg bw (infusion) in cats. In mice, the following other LD$_{50}$-values are reported: 1.6 mg/kg bw for intratracheal, 7.8 mg/kg bw for intramuscular and 60 to 75 mg/kg bw for intragastric administration, while rectal administration of doses up to 280 mg/kg bw and local application of doses up to 12 mg/kg bw did not cause signs of acute toxicity.

5. Intragastric administration for 60 days to rats of 500 mg/kg bw of an extract (not defined) of Capsicum fruits (species not given) or 50 mg/kg bw of capsaicin caused reduced rate of growth. After one month a pronounced reduction of the following parameters was observed: urea in plasma, glucose, phospholipids, triglycerides, total cholesterol, free fatty acids, glutamic-pyruvic transaminase and alkaline phosphatase. The effect of the extract was more pronounced than that of capsaicin.
Inclusion of 5% "red pepper" or 0.015% capsaicin in the standard diet of rats for a period of eight weeks caused reduction of body weight and lipogenic enzymes. The fructose-induced increase of serum triglycerides was also diminished.

6. Oral administration of 1 mg/kg bw of capsaicin (solution in ethanol) to rats for 3 to 9 months caused loss of the mucous layer of the stomach, degeneration of mucus producing cells, oedemas of the mucosa and submucosa as well as stomach bleedings.

Application to the tongues of mice for more than 16 months of 10 µl twice a week of an ethanolic chili extract (corresponding to twice 25 µg capsaicin) caused loss of weight, increased mortality and histo-pathologic changes of the tongue, the stomach, the liver and the kidneys.

Rats receiving 50 mg/kg bw/day of capsaicin or a paprika-extract corresponding to 5 mg/kg bw/day of capsaicin suffered a significant reduction of body weight, which means that the extract was considerably more active than pure capsaicin.

Chronic administration of capsicum extract (corresponding to 0.5 µg capsaicin/kg) to hamsters has been reported to be toxic. Treated animals did not survive beyond 17 months whereas all untreated controls survived beyond this period. In addition, eye abnormalities were observed in the treated animals. This effect was attributed to the depletion of substance P in primary afferent neurones by capsaicin, causing a loss of corneal pain sensation and subsequently the loss of protective corneal reflexes.

7. No information was submitted on the effects of Capsici fructus acer or capsaicin on the effects on reproduction and fertility as well as on teratogenicity.

8. Summaries in published literature are partly contradictory regarding the mutagenic potential for capsaicin and extracts of the fruit.

9. Application of 10 µl twice a week of an ethanolic chili extract (corresponding to twice 25 µg capsaicin) on the tongues of mice caused an increased frequency of formation of tumours in the stomach and the liver. The increase was, however, not statistically significant. Not significant increase in the frequency of formation of adenocarcinoma in duodenum was observed in mice fed 0.06 to 1% capsaicin in the diet. Capsaicin acts as a cocarcinogen to N-ethyl-N'-nitro-N-nitrosoguanidin, dimethyl-nitrosamin acetate and hexachloro-cyclohexane. The carcinogenic potential of Capsici fructus acer thus appears not to be of concern for the consumer.

10. Allergic reactions can occur but are rare. No further information on immunotoxicity was provided.

11. The following information on toxicity in humans is available. Ingestion of 10 g of red chillies (capsaicin content not given) by controls and duodenal ulcer sufferers has been reported to have no significant effects on acid or pepsin secretion, or on sodium, potassium and chloride concentrations in the gastric aspirate. No apparent change (qualitative or quantitative) in mucous and no gastric mucosal erosion was evident. However, there are reports that capsicum causes increased acid concentration and DNA content (indicating exfoliation of epithelial cells) of gastric aspirates in both control subjects and patients with duodenal ulcers. As no dosage is reported in the latter cases the results can not be compared.
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:

- *Capsici fructus acer* is of low acute oral toxicity,
- *Capsici fructus acer* is used as a spice in human food,
- Capsaicin is rapidly absorbed and excreted in laboratory animals,
- *Capsici fructus acer* is used only 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;

The Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for *Capsici fructus acer* and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

<table>
<thead>
<tr>
<th>Pharmacologically active substance(s)</th>
<th>Animal species</th>
<th>Other provisions</th>
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<tbody>
<tr>
<td><em>Capsici fructus acer</em></td>
<td>All food producing species</td>
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