



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CARDIOSPERMUM HALICACABUM

SUMMARY REPORT

1. *Cardiospermum halicacabum* (synonym: *Cardiospermum microcarpum*) is a plant of the family *Sapindaceae*. *Cardiospermum* is a climbing plant widespread distributed in tropical and subtropical Africa and Asia, often found as a weed along roads and rivers. The mother tincture is prepared according to the homeopathic pharmacopoeias by ethanolic extraction of the fresh flowering aerial parts of *Cardiospermum halicacabum*. The whole plant *Cardiospermum halicacabum* contains saponins, traces of alkaloids, flavonoids, proanthocyanidin, apigenin and phytosterols (e.g. stigmasterol). The seeds contain approximately 33% of fatty acids and of these fatty acids about 55% are cyano lipids. The major cyano lipid (49%) is a diester having two fatty acid moieties esterified with 1-cyano-2-hydroxymethyl-prop-2-ene-1-ol followed by a diester derived from 1-cyano-2-hydroxymethyl-prop-2-ene-3-ol (6%). Of the fatty acids, 11-eicosenic acid is with 42% the major one (42%), other chief components of the oil are oleic acid (22%), arachidic acid (10%), linolenic acid (8%), palmitic acid (3%) and stearic acid (2%). In the leaves larger amounts of saponins and alkaloids were found, also (+)-pinitol, apigenin, luteolin and chrysoeriol. The occurrence of esterified fatty acids, pentacyclic triterpenoids various phytosterols and hydrocyanic acid releasing cyano lipids in the mother tincture was confirmed, although at much lower concentrations than in the whole fresh plant. Alkaloids have not been detected in the homeopathic mother tincture. The mother tincture contains a relatively higher amount of flavonoids than the plant.
2. In veterinary homeopathy the mother tincture intended for oral or parenteral use in all food producing species. The use follows the principles of homeopathic therapy where animals are diagnosed on basis of the individual pattern of clinical signs. The recommended maximum parenteral dose in large animals is 10 ml/animal. Corresponding doses in form of tablets, globules or drops are reported to contain lower amounts of *Cardiospermum halicacabum* than the injectable form. Treatment may be repeated but a fixed dose schedule is not common in homeopathy. *Cardiospermum halicacabum* is also used in human homeopathy. In traditional medicine in Africa and Asia, *Cardiospermum halicacabum* is used dermally and orally.
3. The intraperitoneal LD₅₀ of an 95% ethanolic extract of the leaves of *Cardiospermum halicacabum* was reported to be 800 mg/kg bw in mice; a 50% ethanolic extract of the whole plant showed a maximum tolerable dose of 500 mg/kg bw. The dried powdered plant was reported to be without oral toxicity in rats at doses up to 40 g/kg bw. No further data on acute oral toxicity was provided.
4. *Cardiospermum halicacabum* is cyanogenic due to the presence of hydrocyanic acid releasing cyano lipids. The 95% ethanolic extract of the leaves has been reported to produce central nervous system depression in mice at high, near lethal doses (approximately 1000 mg/kg intraperitoneally). On the cardiovascular system the extract caused a fall of blood pressure and bradycardia in rats and anaesthetised dogs (50 mg intravenously). The fall of blood pressure was antagonised partially by atropine and anti-histamine. On guinea pig ileum the extract produced powerful contraction which was partially antagonised by atropine and anti-histamine. An extract

(the dried residues of an ethanolic extract suspended in 2% gum acacia solution) produced mild analgesia and significant anti-inflammatory effects in rats when administered orally. The effective dose was 500 mg/kg bw 1 to 5 hours prior to carrageen treatment. The anti-inflammatory activity of *Cardiospermum halicacabum* was confirmed and it was demonstrated that a fraction rich in triterpenoids was responsible for these effects. The alkaloid fraction of the seeds was reported to show some antibacterial activity (against *Escherichia coli*, *Klebsiella pneumoniae*, *Shigella boydii*, *Salmonella typhimurium*). An aqueous extract of the fruits showed an inhibitory effect on growth of bacteriophages. The seed oil is reported to be an effective insect repellent (*Tribolium castaneum*) at a concentration of 1%.

5. The toxic potential of *Cardiospermum halicacabum* is predominantly connected with the presence of hydrocyanic acid releasing cyano lipids. However, maximum permitted levels for hydrocyanic acid in foodstuffs in the EU occurring either naturally or following the addition of flavourings is 1 mg/kg (except nougat and marzipan or its substitutes where a content of 50 mg/kg is permitted). Residues in food producing animals receiving maximal doses of mother tincture of *Cardiospermum*, which has only very low cyanogenic activity, will not exceed these values. Furthermore the cyanic ion is ingested, in small amounts, by herbivores on a regular basis via feed.
6. In a preliminary risk evaluation procedure by the Committee for Veterinary Medicinal Products (CVMP) considering all defended old substances used in homeopathy in concentrations greater than 1:10 000, the use of *Cardiospermum halicacabum* and its individual constituents was considered as not giving rise to specific health concern. Special emphasis was put on identification of any suspicion pointing to genotoxicity or other potential of serious health effects of plant constituents. Except for the presence of cyanogenic components the information provided and extensive search of published literature did not provide any further evidence for pharmacological or toxicological properties of *Cardiospermum halicacabum* alerting to specific health risks which may result from residues in food producing animals following intended uses.

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:

- *Cardiospermum halicacabum* is used in a small number of individual animals and for non-regular treatments only,
- animals are unlikely to be sent for slaughter during or immediately after treatment,
- residues of hydrocyanic acid which might theoretically be released from cyano lipids present in the plant were considered to be below maximum limits established for plant derived foodstuffs in the EU,
- apart from the presence of cyanogenic lipids, *Cardiospermum halicacabum* and individual constituents thereof do not give rise to specific consumer health concern which may result from the use in veterinary homeopathy;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for *Cardiospermum halicacabum* 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
<i>Cardiosperm halicacabum</i>	All food producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias at concentrations corresponding to the mother tincture and dilutions thereof only