



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PRUNUS LAUROCERASUS

SUMMARY REPORT

1. *Prunus laurocerasus* L. (synonym: *Laurocerasus officinalis*; laurel cherry) is a plant of the family *Rosaceae*. *Prunus laurocerasus* is a bush originating from Asia and the Balkans, which is nowadays cultivated in Southern and Middle Europe as a garden and hedge plant. The homeopathic mother tincture is prepared according to homeopathic pharmacopoeia by ethanolic extraction of the fresh leaves of *Prunus laurocerasus*.

The leaves of *Prunus laurocerasus* contain 1 to 2.5% cyanogenic glycosides. The main cyanogenic glycosides are prunasin (L(-)-mandelonitrile- β -D-glucoside) and sambunigrin (L(+)-mandelonitrile- β -glucoside). Approximately 50 to 210 mg hydrocyanic acid can be liberated from 100 g fresh leaves. Further constituents are essential oils (0.05%), ursolic acid (1%), flavonoids like kaempferol and quercetin, caffeic- and p-coumaric acid, enzymes like prunase, D-oxynitrilase and a β -glucosidase, which splits the glycosides into a sugar and a cyanohydrine component. The latter is unstable and dissociates to hydrocyanic acid and a carboxylic compound. Additional constituents of the leaves are lipids (3.5%) and ash (5 to 7%) with the trace elements arsenic, copper, zinc, manganese, aluminium.

2. In veterinary homeopathy the 1:1000 dilution is 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 for large animals is 10 ml/animal. Corresponding doses of 1:1000 in form of tablets, globules or drops are reported to contain lower amounts of *Prunus laurocerasus* than the injectable form. Treatment may be repeated but a fixed dose schedule is not common in homeopathy.

Prunus laurocerasus is also used in human homeopathic medicine as the mother tincture as well as in lower concentrations. The use of the mother tincture and the 1:10 dilution in infants and children, as well as during pregnancy is contraindicated.

3. *Prunus laurocerasus* is acutely toxic. The toxicity of the plant is attributed to hydrocyanic acid liberated from the cyanogenic glycosides. The production of hydrocyanic acid in humans and animals after intake of *Prunus laurocerasus* is partly due to hydrolytic cleavage of cyanogenic glycosides by endogenous plant enzymes but to a greater extent to bacterial β -glucosidases formed in the gastrointestinal tract. Hydrocyanic acid inhibits the enzymes necessary for transport of oxygen from blood to tissues. It has a strong affinity to cytochrome oxidase-Fe³⁺, forming a link which results in immediate inhibition of cellular respiration. The resulting energy deficiency can cause a break down of the central nervous system and death ensues from generalised cytotoxic anoxia.

4. Specific information on pharmacokinetics and metabolism of *Prunus laurocerasus* was not available. However, it is well known that oral intake of the leaves of *Prunus laurocerasus* yields larger amounts of absorbed hydrocyanic acid than parenteral administration of plant preparations (*aqua laurocerasi*). While free hydrocyanic acid is rapidly absorbed from all tissues (within seconds up to a few minutes), the absorption of hydrocyanic acid from ingested plant material is reported to be slow and incomplete due to suboptimal pH-conditions for hydrocyanic acid liberation in the gastrointestinal tract (optimum for β -glucosidases: pH 5 to 6). In mammals hydrocyanic acid is detoxified by combination of the cyanide ion with endogenous thio-sulphate to thio-cyanate, which is then excreted in the urine. Humans are able to detoxify about 1 mg hydrocyanic acid per hour. After orally administration of prunasin (D,L-mandelonitrile- β -D-glycoside) to rats, a rapid absorption of the glycoside from the gastrointestinal tract was seen with the highest absorption rate of 53.4% within 165 minutes. About 30 to 45% of the administered glycoside was excreted within 24 hours.
5. Cyanogenic glycosides such as prunasin constitute the toxic principle of *Prunus laurocerasus*. The oral LD₅₀-value of D,L-mandelonitrile- β -D-glycoside (prunasin) in rats was determined as 560 mg/kg bw. Death of sheep and cattle after ingestion of *Prunus laurocerasus* leaves has been reported. In general, ruminants are more sensitive to cyanogenic glycosides because the near neutral pH in their stomachs favours the release of hydrocyanic acid. The lethal dose of hydrocyanic acid in mammals is generally considered to be 1 mg/kg bw. Intoxications from *aqua laurocerasi*, an extract obtained by hydrodistillation of cut *Prunus laurocerasus* leaves, were reported in humans. The mean lethal dose of orally administered *aqua laurocerasi* was about 60 mg/person. In a case report 17 drops of *aqua laurocerasi* were sufficient to cause lethal intoxication. Cyanogenic glycosides (laetrile) have been considered to be effective in the treatment of malignant tumours. However, due to severe adverse toxic effects of laetrile, the drug is no longer recommended in anti-cancer therapy.
6. Risk assessment with respect to cyanogenic compounds contained in *Prunus laurocerasus* may be based on the following considerations. In veterinary homeopathy a 1:1000 dilution of the mother tincture is used, containing a maximum of 0.1% of plant material. A maximum of 200 mg hydrocyanic acid/100 g of fresh leaves can be liberated. Therefore, the maximum amount of hydrocyanic acid available from cyanogenic glycosides of the 1:1000 dilution is 2 μ g/g or ml, respectively. A maximum (intravenous) dose of 10 ml administered to large animals (500 kg bw) would amount to a total of 20 μ g (liberated) hydrocyanic acid. Assuming no further detoxification and excretion a standard edible meat portion would contain 0.04 μ g hydrocyanic acid. In a similar calculation for milk, based on a daily milk production of 20 litres by a 500-kg cow and assuming a proportion of 2% of the dose excreted into milk, worst case residues in milk would amount to 0.04 μ g/l.
7. In the European Union maximum limits have been established for hydrocyanic acid in foodstuffs either naturally or following the addition of flavourings prepared from natural raw material. These limits are 1 mg/kg for foodstuffs and beverages, except nougat and marzipan or its substitutes where a content of 50 mg/kg is permitted. For canned stone fruits a maximum limit of 5 mg/kg has been established. The calculated worst-case amounts of hydrocyanic acid in foodstuffs from animals treated with *Prunus laurocerasus* in a 1:1000 dilution are insignificant when compared to the limits established for plant derived foodstuffs in the European Union. It should also be borne in mind that the cyanide ion is ingested by herbivores in small amounts on a regular basis via feed.
8. With the exception of cyanogenic components, further information made available and systematic search of published literature did not provide any further evidence for pharmacological or toxicological properties of *Prunus laurocerasus* and its constituents alerting to specific health risks which may result from residues in food producing animals following the intended uses. Special emphasis was put on identification of suspicion pointing to genotoxicity or other potential of serious health effects of plant constituents. In a preliminary risk evaluation procedure by the Committee for Veterinary Medicinal Products, considering all defended old substances used in veterinary homeopathy in concentrations greater than 1:10 000, the use of *Prunus laurocerasus* in a 1:1000 dilution and its individual constituents (with the exception of cyanogenic components) was considered as not giving rise to specific health concerns.

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:

- *Prunus laurocerasus* is used only as a diluted homeopathic extract not exceeding concentrations of one part per thousand,
- worst-case residues of hydrocyanic acid in meat or milk, which may result from the presence of cyanogenic glycosides in homeopathic preparations of *Prunus laurocerasus*, were considered negligible compared to maximum limits established for plant derived foodstuffs,
- *Prunus laurocerasus* is used only in a small number of individual animals for 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 constituents of *Prunus laurocerasus* in a dilution of 1:1000 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>Prunus laurocerasus</i>	All food producing species	For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias, at concentrations in the products not exceeding one part per thousand only