



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PHYTOLACCA AMERICANA

SUMMARY REPORT

1. *Phytolacca americana* L., synonyms *Phytolacca decandra*, Pokeweed, is a plant of the family *Phytolaccaceae*. The homeopathic mother tincture is prepared according to the German Homeopathic Pharmacopoeia (HAB, method 3a) by ethanolic extraction of the fresh roots of *Phytolacca americana*. In veterinary homeopathy a dilution of 1:1000 is used for treatment of food producing animals. The use follows the principles of homeopathic therapy where animals are diagnosed on the basis of the individual pattern of clinical signs. The recommended maximum parenteral dose is 10 ml for large animals (assumed body weight of 500 kg). Corresponding doses for oral treatment with tablets, drops or globules contain lower amounts of plant extract than the injectable form. Dosing may be repeated but a fixed dosage schedule is not common in homeopathy.

In human homeopathy *Phytolacca americana* dilutions including the mother tincture are used. The medicinal drug derived from dried *Phytolacca* roots is used orally in human phytotherapy at daily doses of 60 to 100 mg. Up to 1 g of the dry roots may be used orally as an emetic.

2. Root extracts of *Phytolacca americana* can be characterised by a broad spectrum of plant constituents including some substances of possible pharmacological or toxicological relevance like the triterpene saponins, several mitogenic acting cysteine rich glycoproteines – lecithins also known as pokeweed mitogens (PWM), and an antiviral acting protein PAP-R (pokeweed antiviral protein from root) with a molecular weight of 29 kDa. *Phytolacca americana* contains about 8 triterpenoid saponins (phytolaccosides) with phytolaccoside E being the main saponin. Identified genins are esculentic acid, jaligonic acid and phytolaccagenic acid. Further constituents are histamine (0.13% to 0.16%), γ -amino butyric acid, spinasterol, starch, saccharose and potassium salts (e.g. potassium nitrate).
3. Various pharmacological effects have been observed for *Phytolacca americana* root extracts or isolated constituents thereof. The triterpene saponins appear to be predominantly responsible for these effects: The triterpene saponins are strong irritants. They can exhibit antifungal activity. Spermicidal activity has also been reported for saponin extracts from *Phytolacca americana*. Water insoluble triterpene saponin fractions were found to exert antiinflammatory activity on acute oedema in rats and in mice. An intraperitoneal dose of 15 to 30 mg/kg bw of crude saponins reduced carragenin-induced paw oedema in rats by 50%.

Pokeweed antiviral protein (PAP), a glycosidase which can inactivate ribosomes, has potent antiviral activity against many plant and animal viruses, including human immunodeficiency viruses. *In vitro* studies showed that pokeweed antiviral protein inhibits protein synthesis of lysates of rabbit reticulocytes with an IC_{50} of 0.05 nM. The effect is less pronounced on intact fibroblasts (IC_{50} : 0.07 μ M) and HeLa cells (IC_{50} : 3.3 μ M). *Phytolacca* mitogens were found to have a stimulating effect on the immune system, especially on the proliferation of T- and B-lymphocytes.

4. Pharmacokinetic information on the extract of *Phytolacca americana* or its constituents were not provided. As regards constituents of *Phytolacca americana*, it may be noted that generally compounds of the class of saponins are not significantly absorbed in the gastrointestinal tract. Absorption and systemic bioavailability of native, i.e. intact pokeweed proteins and glycoproteins is considered limited.
5. Data on acute intraperitoneal toxicity of *Phytolacca* saponin extracts were reported with LD₅₀ values of 181 mg/kg bw in the mouse, and of 208 mg/kg bw in the rats. For the isolated pokeweed antiviral root protein the LD₅₀ was 1.2 mg/kg bw for female mice, 2 days after intraperitoneal application. Data on acute oral toxicity were not available.
6. Specific studies on repeated dose toxicity or reproductive effects including teratogenicity of *Phytolacca americana* root extracts or its constituents have not been provided.
7. No specific studies on genotoxic properties of *Phytolacca americana* were provided. Referring to the main toxic constituents, i.e. saponins and *Phytolacca* mitogens, published data provided no indication for genotoxic properties of these substances. A number of saponins (more than 10), isolated from related plants, e.g. *Phytolacca dodecandra*, were found to be non-mutagenic in *Salmonella typhimurium* strains TA 97, TA 98, TA 100 and TA 102 (*Salmonella*-microsomal assay) in absence and presence of metabolic activation.
8. No studies on carcinogenic properties of *Phytolacca americana* were provided.
9. The pokeweed mitogen was found to be effective on the immune system by stimulating cell proliferation of different lymphocyte classes. Electrophoretic investigations of sera of poisoned patients showed an unspecific increase of immunoglobulines and of the eosinophile granulocytes. Furthermore, phagocytosis of thrombocytes could be detected.
10. Despite the fact that all parts of *Phytolacca americana* may have acute toxic effects, the plant is occasionally used as vegetable and for preparation of poke root tea in North America, mainly by Indians. Therefore, poisoning incidents were reported rather frequently but symptoms were normally mild and cases of death rare. There are however some reports of intoxications with fatal outcome. Oral intake of the root extract mainly causes disorders of the gastrointestinal tract associated with vomiting and severe diarrhoea. In a case report, symptoms of a complete but reversible tetanus have been reported after oral intake of about 4 g of the root tincture by a boy. Intoxication with the root extract via skin lesions and/or mucous membrane injuries is characterised by various morphological changes of the blood count, an increase of immature basophile lymphocytes and plasma cells and an unspecific increase of immunoglobuline G. Additionally phagocytosis of thrombocytes could be observed. Adverse effects for the human homeopathic preparation of *Phytolacca americana* were not reported and there are no contraindications as regards all uses including the mother tincture.
11. It was not possible from the available information to establish a complete pharmacological and toxicological profile including NOELs and ADI for *Phytolacca americana* extracts and its constituents. Consumer safety considerations may be based on some worst-case assumptions: In the absence of data, it is assumed that the root material of *Phytolacca americana* contains an arbitrarily high content of 30% of constituents of possible concern (i.e. saponins, mitogenic acting glycoproteins, antiviral acting protein) and that all these constituents are completely soluble upon ethanolic extraction. An 1:1000 dilution then would contain up to 0.3 mg/ml of these constituents. A maximum intravenous dose of 10 ml given to large animals (6 µg/kg bw at an assumed body weight of 500 kg) would amount to a total of 3 µg of residues in a standard edible meat portion. In a similar calculation for milk assuming a very high proportion of 2% of the dose excreted into milk, the maximum residues would amount to 3 µg/l (based on a milk production of 20 l/day by a 500 kg cow). If one considers further, that all constituents of possible concern are of limited oral absorption and/or systemic bioavailability, the estimated worst case residues in the low µg range can be considered negligible, when compared to any levels of possible consumer health concern.

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:

- *Phytolacca americana* is used as a diluted extract not exceeding one part per thousand prepared according to homeopathic pharmacopoeias,
- oral absorption and systemic bioavailability of *Phytolacca americana* constituents of possible concern (saponins, proteins, glycoproteins) is considered limited,
- *Phytolacca americana* is used in a small number of individual animals for non-regular treatments in accordance with the principles of homeopathic therapy,
- 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 homeopathic preparations of *Phytolacca americana* at concentrations not exceeding one part per thousand 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>Phytolacca americana</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.