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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

THUJA OCCIDENTALIS

SUMMARY REPORT

1. *Thuja occidentalis L.*, synonym *Abor vitae*, is a plant of the family *Cupressaceae* which has been originally cultivated in North America, but is nowadays a common garden plant in Middle and Southern Europe. The homeopathic mother tincture is prepared by ethanolic extraction according to the German Homeopathic Pharmacopoeia (HAB, method 3a) of the fresh leaves and twigs obtained from *Thuja occidentalis* in late spring. In veterinary homeopathy a dilution of 1:100 is used for treatment of food producing animals. The use of the preparation follows the principles of homeopathic therapy where animal are diagnosed on basis of the individual pattern of clinical signs. The recommended maximum parenteral dose is up to 10 ml for large animals (assumed body weight of 500 kg). Corresponding doses for oral treatment with drops, tablets, 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 homeopathic medicine *Thuja occidentalis* is used in form of the mother tincture and dilutions thereof. *Thuja occidentalis* is also used in traditional human phytotherapy.

2. *Thuja occidentalis* leaves and twigs are rich in essential oils, mainly terpenes with thujone being the predominant constituent. The leaves of *Thuja occidentalis* contain 0.4% to 1% essential oils. The total content of essential oils in dried young twigs was reported as 1.4 to 4%. The content of thujone in dried twigs was determined as 7.6 mg/g (0.76%), consisting of 85% α-thujone and 15% of the more toxic β-thujone. Further monoterpenoids are α-pinene, myricene, α-terpinene, limonene, γ-terpinene, terpinolene, fenchone, and traces of sabinene, but also camphene, borneol and thulylalcohol have been identified. Other constituents are lignans, flavonoids like quercetin, kaempher glycosides and myricetine, approximately 1.3% tannic acid and 4% thujapolysaccharides and proteins.

3. The pharmacodynamic properties of *Thuja occidentalis* are mainly attributed to the essential oils, especially thujone. Thujone is a strong irritant and has cytotoxic properties. Possible effects are various and are generally considered to include antimicrobial, anthelmintic, uterine stimulant as well as psychedelic activity. Also antidot effects to opium and other central nervous system depressant poisons have been described. Besides these effects, water soluble extracts of *Thuja occidentalis* with a high content of thujapolysaccharides and proteins were reported to have immune stimulating potency. *In vitro* studies showed an enhancement of proliferating T-lymphocytes and an increase of cytokine 2 distribution. Furthermore, thujapolysaccharides seem to have antiviral properties. It was found to inhibit the replication of HIV-1 virus *in vitro* and enhances *in vivo* haematopoietic progenitor cells recovery in sublethally irradiated mice.

4. Specific pharmacokinetic information for extracts of *Thuja occidentalis* was not provided. The lipophilic character of the constituents of concern like thujone is indicative of a relatively good dermal resorption from mucous membranes and even from intact skin. Thujone is predominantly eliminated via kidneys and lungs.

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5. As regard the constituent thujone LD_{50} values were given as 87.5 mg/kg bw after subcutaneous administration in mice and 240 mg/kg bw after intraperitoneal administration to rats. For humans, an oral intake of 1.25 mg/kg bw (about 75 mg/person) was reported to be without adverse effects.

6. Data on repeated dose toxicity of *Thuja occidentalis* extracts have not been provided.

7. No studies on reproductive effects including teratogenicity of *Thuja occidentalis* extracts were available. The essential oil obtained by steam distillation of *Thuja occidentalis* species rich in essential oils was reported to cause toxicity including malformations of chicken embryos.

8. *Thuja* extracts have been reported to give negative response in the *Salmonella*-microsomal assay (strains TA 98 and TA 100) with and without metabolic activation. There was some indication of antimutagenic properties of *Thuja occidentalis*. *In vitro* investigations have demonstrated that an ethanolic extract from *Thuja occidentalis* has a geno-protective effect on cadmium chloride-treated root tip meristems of *Pisum sativum*. The extract induced higher mitotic activity and a decrease of chromosomal aberrations correlated with the duration of treatment. In another study it could be shown that the extract from mugwort (*Artemisia asiactica nakai*) leaves (also containing thujone) reduced the mutagenicity of aflatoxin B1. It was reported that ethanolic extracts have an inhibitory effect on ^{3}H-benz[a]pyrene binding and metabolic activation by rat liver microsomal proteins. *Thuja occidentalis* and thujone have not been associated with genotoxic activity so far.

9. Studies on carcinogenic activities of *Thuja occidentalis* were not provided.

10. No specific studies on immunotoxicity were provided. An allergic contact dermatitis to *Thuja occidentalis* has been reported after a 3-week application of the homeopathic mother tincture. The possible allergenic constituent of *Thuja* has not been identified until now and may be related to a group of resin acids.

11. In humans, *Thuja* extracts were used in folk medicine as a contraceptive and an abortificiant. In cases of overdosing and abuse, the oral intake of *Thuja* extracts induced severe metabolic disturbances especially degenerative disorders of the liver. The intoxication was accompanied by irritant effects on the mucous membranes of the gastro-intestinal tract, severe and long lasting contractions also of the uterus and severe metabolic disorders due to liver and kidney lesions with fatal outcome. However, the symptoms of poisoning after oral intake of plant material are normally mild. Infants who ingested leaves or small twigs of *Thuja occidentalis* showed mild gastrointestinal disorders and vomiting. The homeopathic *Thuja occidentalis* mother tincture and the 1:10 dilution, when ingested orally, should be taken together with water due to the strong irritant properties to mucous membranes. The use of mother tincture and the 1:10 dilution in pregnancy is contraindicated. In traditional phytotherapy, recommended oral doses of the drug consisting of dried young twigs are for instance 1 to 2 g, corresponding to up to 40 to 80 mg thujone, 3 times a day. Repeated intake of thujone-containing beverages (e.g. absinth) was reported to cause permanent disorders of the central nervous system.

12. It was not possible from available information to establish a complete pharmacological and toxicological profile including NOELs and an ADI for *Thuja occidentalis* and its constituents. Consumer safety assessment may be based on the following considerations: For *Thuja occidentalis*, the maximum content of total essential oils in the dried younger twigs has been reported with up to 4% (40 mg/g). If one assumes in a worst case that the content of essential oils in the homeopathic mother tincture equals that measured in dried twigs and further, that all of the essential oil consists exclusively of thujone, the homeopathic 1:100 dilution would contain 1.2 mg thujone/ml, which corresponds to 12 mg in a maximum intravenous dose (10 ml) for large animals (24 µg/kg bw based on an assumed body weight of 500 kg). Assuming no metabolism or excretion, this dose would lead to an amount of 12 µg thujone in a standard edible meat portion. A similar calculation can be done for milk. Assuming a very high proportion of 2% of the dose excreted into milk, worst case residues would amount to approximately 12 µg/l (based on a milk production of 20 l/day by a 500 kg cow).

13. These calculated residues in animal derived food appear to be negligible compared to the human exposure to thujone and thujone containing essential oils from other sources. Thujone, the major constituent of *Thuja occidentalis* of possible concern is a terpene, which occurs in significant quantities in the essential oil fraction of many plants, which are part of the human diet (e.g. *Salviae, Artemisiae*). *Salviae folium*, for instance, is widely used as spice and for preparation of teas. The essential oil of *Artemisia pontica* contains approximately 30% thujone and is used for the production of vermouth wine.

    For thujone in plant derived food commodities, present either naturally in the essential oils of the foodstuffs or following the addition of flavourings prepared from natural raw materials, maximum limits have been established in the European Union. These limits are 0.5 mg/kg for foodstuffs and beverages, except Salvia tea and bitter alcohols, where contents of 35 mg/kg and 25 mg/kg, respectively, are permitted. The calculated worst-case amounts in food from animals are at least 40-fold lower than the lowest maximum limit established for plant derived foodstuffs. *Salvia folium* and *Absinthium extract*, which contain thujone in similar or even higher quantities than the plant *Thuja occidentalis*, have already been included into Annex II of Council Regulation (EEC) No 2377/90 for food producing animals.

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:

- *Thuja occidentalis* is used as a diluted extract not exceeding one part per hundred,
- the major constituents of possible concern like the thujone containing essential oils are natural components present in human food commodities derived from plants or in flavourings used for food production,
- calculated worst-case residues of thujone in meat or milk were considered negligible compared to maximum limits established for plant derived foodstuffs or following use of flavourings,
- *Thuja occidentalis* is used 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 homeopathic preparations of *Thuja occidentalis* at concentrations not exceeding one part per hundred 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
Thuja occidentalis	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 hundred only.