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Committee on Herbal Medicinal Products (HMPC)

# Assessment report on *Eucalytus globulus* Labill., *Eucalyptus polybractea* R.T. Baker and/or *Eucalyptus smithii* R.T. Baker, aetheroleum

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Draft

| | |
|---|---|
| Herbal substance(s) (binomial scientific name of the plant, including plant part) | *Eucalyptus globulus* Labill., *Eucalyptus polybractea* R.T. Baker and *Eucalyptus smithii* R.T. Baker, folium recens aut summitas recens |
| Herbal preparation(s) | aetheroleum |
| Pharmaceutical form(s) | Herbal preparation in liquid or solid dosage forms for oral use.<br>Herbal preparation in liquid dosage forms for inhalation or as bath additives.<br>Herbal preparation in liquid or semi-solid dosage forms for cutaneous use. |
| Rapporteur | |
| Assessor(s) | |

Note: This draft assessment report is published to support the release for public consultation of the draft Community herbal monograph on *Eucalytus globulus* Labill., *Eucalyptus polybractea* R.T. Baker and/or *Eucalyptus smithii* R.T. Baker, aetheroleum. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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# 1. Introduction

## *1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof*

- Herbal substance(s)

The herbal substance consists of the fresh leaves or fresh terminal branchlets of various species of Eucalyptus rich in 1,8-cineole (from which the oil is obtained by steam distillation and rectification).

Early edition of the Deutsche Arzneibuch [DAB 6 1951] only referred to *Eucalyptus globulus* Labill., while later editions [DAB 7 1968] referred to other species rich in 1,8-cineole, such as *Eucalyptus polybractea* R.T. Baker (syn. *Eucalyptus fruticetorum* F. MUELLER) and *Eucalyptus smithii* R.T. Baker.

The three species mainly used are *Eucalyptus globulus* Labill., *Eucalyptus polybractea* R.T. Baker and *Eucalyptus smithii* R.T. Baker [European Pharmacopoeia 2012, Real Farmacopea Espanola 2005, ESCOP 2003, Pharmacopée Française 1976, Blaschek *et al.* 2007]. Eucalyptus belongs to the family of Myrtaceae, subfamily Myrtoideae. There are more than 700 species of the genus.

**Occurrence**

Eucalyptus is indigenous to Tasmania and south-eastern Australia. It is cultivated in many parts of the world. The main producer regions of *Eucalyptus globulus* Labill. are the coasts of Spain, Black sea and the Caucasus. *Eucalyptus smithii* R.T. Baker is cultivated in Brazil, Guatemala, Hawaii and at the French Atlantic coast as well as Caucasus. *Eucalyptus polybractea* R.T. Baker occurs only in Australia especially in Victoria and New South Wales [Blaschek *et al.* 2007].

**Biology**

There are several species of Eucalyptus, while *Eucalyptus globulus* is the most popular in terms of cultivation and medicinal use. The Eucalyptus trees with the highest 1,8-cineole content (80-95%) are *E. kochii* and *E. polybractea* [Clare 2010].

Eucalyptus trees are evergreen with leathery oil glands covered leaves. The leaves of *Eucalyptus globulus* Labill. are ensiform or sword-shaped, 15-30 cm up to 40 cm (6 to 12 inches ) long, 5 cm (2 inches) wide, bluish-green in hue, which are alternate and vertical [Blaschek *et al.* 2007]. The leaves are studded with brown lenticels and colourless glands containing fragrant volatile oil. Investigations by Daroui-Mokaddem *et al*. [2010] yielded an amount of 2.5% volatile oil derived from fresh leaves by hydrodistillation, while Cimanga *et al*. [2002] had found only 1.87%.

*Eucalyptus polybractea* R.T. Baker is a small, deeply rooted, perennial tree with smooth and fibrous bark near the trunk base. Its leaves are disjunct and linear to narrow-lanceolate shaped 4-10 cm (1.5–3.9 inches) long and 0.5-3 cm (0.2–1.2 inches) wide. Juvenile leaves are glaucous while adult ones are grey-green. The leaves may contain 1.2 to 2.5% of volatile oil [Blaschek *et al.* 2007].

*Eucalyptus smithii* R.T. Baker is a medium sized up to 46 m tall tree. Its bark is at the lower part deeply fissured and in the upper parts smooth and white. Leaves are green or bluish-green, narrow-lanceolate shaped 3-18 cm (1.2–7.1 inches) long and 1-3 cm (0.4–1.2 inches) wide. Leaves contain 1.2 to 2.2% volatile oil [Blaschek *et al.* 2007].

**Constituents**

The main constituent of the volatile oil derived from fresh leaves of Eucalyptus species is 1,8-cineole. The reported content of 1,8-cineole varies for *Eucalyptus globulus* oil between 70-85%, 48.6%, 54-61% and 54-95% [Wichtl 2004, Daroui-Mokaddem *et al*. 2010, Betts 2000, WHO monographs 2002].

Beside 1,8-cineole, the oil contains monoterpenes such as cymene, α-pinene, β-pinene and limonene, geraniol and camphene [Blaschek *et al.* 2007]. The WHO monograph [2002] describes additionally aromadendrene, cuminaldehyde, globulol and pinocarveol as constituents.

Silvestre *et al*. [1997] have found that younger leaves tend to have a higher oil-content than mature ones. Content in 1,8-cineole showed a complex variation along the seasons, but mature leaves always have higher contents of 1,8-cineole. It was not possible, from the data, to establish a relation between the biochemistry of the plants and the season of the year or the geographic location.

Betts [2000] analysed the volatile constituents from fresh leaves of *Eucalyptus globulus* Labill. using the solid-phase microextraction fibre method to absorb the volatiles from headspace. These investigations, using gas chromatographic-FID and MS for identification, showed that fresh leaves of *Eucalyptus globulus* gave only 54-61% 1,8-cineole, 19.5-24.3% α-pinene, 6.7-9.1% limonene and 2.1-5.4% α-terpinyl acetate and 3.6-7.7% sesquiterpenes. The author attributed the differences observed among the different preparation methods to potential hydrolyses during steam distillation.

According to the investigations by Cimanga *et al.* [2002], it was shown that fresh leaves of *E. globulus* contain only 1.87% volatile oil with 35.7% 1,8-cineole.

In 1968 the botanical species *Eucalyptus polybractea* and *Eucalyptus smithii* were also allowed for the extraction of *Eucalyptus* oil. Their content of essential oil has been reported to be higher than that of *Eucalyptus globulus* [Blaschek *et al.* 2007]. While essential oil obtained from *Eucalyptus polybractea* contained 77-84% 1,8-cineole, its aldehyde content was, compared with other Eucalyptus oils, relatively low [Blaschek *et al.* 2007].

The oil obtained from *Eucalyptus smithii* contains 70-77% 1,8-cineole [Blaschek *et al.* 2007].

- Herbal preparation(s)

The Eucalyptus oil is obtained by steam distillation and rectification of the fresh leaves or fresh terminal branchlets of various *Eucalyptus* species. The oil is a pale yellow or clear liquid with characteristic odour and taste. Its quality is described in a monograph of the European Pharmacopoeia [2012]. The monograph specifies the following contents, analysed by gas chromatography:
- 1,8-cineole: not less than 70.0%,
- α-pinene: 0.05-10.0%,
- β-pinene: 0.05-1.5%,
- sabinene: maximum 0.3%,
- α-phellandrene: 0.05-1.5%,
- limonene: 0.05-15.0% and
- camphor: maximum 0.1%.

The chemical content of Eucalyptus oil obtained from different species has been extensively studied [Juan *et al.* 2011, Goodger *et al.* 2010, Dayal and Ayyar 1986, Baranska *et al.* 2005]. Comprehensive investigations by Juan *et al.* showed that the oil obtained from *E. polybractea* consists of the following compounds: α-pinene (0.2%), p-cymene (4.12%), limonene (1.0%), 1,8-cineole (85.01%), γ-terpinene (0.33%), 4-terpnineol (1.48%), α-terpineol (0.7%), viridiflorol (0.59%) and minor other compounds (6.57%) such as α-thujene, β-pinene, α-terpinene, linalool, spathulenol and 10-epi-γ-eudesmol. Whereas the oil obtained from *Eucalyptus smithii* consists of α-pinene (4.61%), limonene (5.88%), 1,8-cineole (78.49%), γ-terpinene (0.65%), 4-terpnineol (0.6%), α-terpineol (2.48%), β-eudesmol (5.46%) and minor other compounds (1.83%) such as α-thujene, β-pinene, α-terpinene, linalool, spathulenol and 10-epi-γ-eudesmol. The composition of the oil obtained from *Eucalyptus globulus* has not been analysed by Juan *et al.* [2011].

Non-volatile monoterpene glucosides, also conjugated with gallic acid, have also been described as components of the essential oils extracted from the leaves of *Eucalyptus globulus* Labill. and *Eucalyptus polybractea* R.T. Baker [Goodger *et al.* 2009, Hasegawa *et al*. 2008].

- Combinations of herbal substance(s) and/or herbal preparation(s) as ingredients of traditional combination herbal medicinal products.

Eucalyptus oil is often marketed in combination products with other herbal substances/preparations, in varied pharmaceutical forms. Examples:
- ointments: combinations with peppermint oil, juniper oil, methyl salicylate, menthol, levomenthol, turpentine oil camphor and fennel oil;
- lozenges: combinations with benzalkonium chloride, levomenthol, peppermint oil, thymol;
- nasal drops: combination with α-tocopherol acetate, pine oil, peppermint oil, thymol and guaiazulene;
- gastroresistant capsules: combinations with the oil of *Citrus sinsesis* and *Citrus limonum*.

## *1.2. Information about products on the market in the Member States*

As indicated in the 'Regulatory status overview' (page 9), several Member States have only combination products on their market, some have no products containing Eucalyptus oil. Only Germany has authorised Eucalyptus oil products with a "well-established use indications".

**Use in Germany**

Bath additives, oral capsules (soft or gastro-resistant), ointments as well as the oil, diluted or undiluted, are available for the external or oral treatment of chronic catarrh of the upper respiratory tract, common cold symptoms of upper respiratory tract with persisting mucus. Ointments, undiluted oil and bath additives are also available for the external treatment of rheumatic complaints. Eleven products have been marketed in Germany for more than 30 years, 6 products have been marketed less than 30 years but at least 15 years. They are comparable (concerning pharmaceutical form and posology) to the products that are more than 30 years on the German market. Additionally 8 products are on the German market for less than 15 years. There are also a lot of comparable products, that have previously been marketed for a long time but which are not on the market anymore for several reasons. These products (marked with asterisks) have also been included in the table 1 below.

Table 1: Eucalyptus oil containing products on the German market for more than 15 years

| **posology** | **patient group** | **indication** |
|---|---|---|
| **since 1976** | | |
| **bath additive** (cutaneous administration) | | |
| 2.6-3.9 g pure oil/100 l water[#] | adults and adolescents over 12<br>Contraindication: <2 years | treatment of chronic catarrh of the upper respiratory tract |
| 1.5-2.9 g pure oil/100 l water[#] | adults and adolescents over 12 | colds symptoms of upper respiratory tract with persisting mucus |
| 2 g pure oil/100 l water[#] | Contraindication: <2 years | cold symptoms of upper respiratory tract |
| 4-6 g pure oil/100 l water[#] | Contraindication: <2 years | colds symptoms of upper respiratory tract with persisting mucus |
| 1.5-2.9 g pure oil/100 l water[#] | Contraindication: <2 years | treatment of chronic catarrh of the upper respiratory tract |
| 2.1 g pure oil/100 l water[#] | Contraindication: <2 years | treatment of chronic catarrh of the upper respiratory tract |
| 1.7 g pure oil/100 l water[#] | adults and adolescents over 12 | rheumatic complaints |
| 2-4 g pure oil/100 l water[#] | Contraindication: < 2 years*** | rheumatic complaints |
| **Ointment/balm** (cutaneous administration) | | |
| rub a 2-3 cm string (10 g Eucalyptus oil/100 g[##]) 4 times a day on chest and back | Contraindication: <2 years*** | colds symptoms of upper respiratory tract with persisting mucus |
| A thin layer on affected areas or aching parts (10 g Eucalyptus oil/100 g) 2-3 times a day | Contraindication: <2 years*** | rheumatic complaints |
| **soft capsule** (oral administration) | | |

| | | |
|---|---|---|
| 100-200 mg oil 3 times a day = 300-600 mg (gastro-resistant) | adults and adolescents over 12 | colds symptoms of upper respiratory tract with persisting mucus |
| 100-200 mg oil 3 times a day = 300-600 mg | adults and adolescents over 12 | colds symptoms of upper respiratory tract with persisting mucus |
| 200 mg oil 2-3 times a day = 400-600 mg | adults and adolescents over 12 | colds symptoms of upper respiratory tract with persisting mucus |
| **since 1976 including German Standardzulassung 1996-2013****** | | |
| **pure oil** (cutaneous administration) | | |
| Some drops (undiluted oil)<br>I: on chest and back<br>II: on affected areas or aching parts | Contraindication: <2 years | I) common colds symptoms of upper respiratory tract with persisting mucus<br>II) rheumatic complaints |
| pure oil (inhalation) | | |
| 3-8 drops in 250 ml hot water | Contraindication: <2 years | common colds symptoms of upper respiratory tract with persisting mucus |
| **since 1992** | | |
| **ointment (cutaneous administration)** | | |
| 2-12 years:<br>3 cm (10 g Eucalyptus oil/100 g[##]) 2-3 times a day<br>over 12 years:<br>6 cm (10 g Eucalyptus oil/100 g[##]) 2-3 times a day<br>on affected areas or aching parts | Contraindication: <2 years | rheumatic complaints |
| **since 1995** | | |
| **soft capsule** (oral administration) | | |
| 300 mg 2 times a day = 600 mg (gastro-resistant) | adults and adolescents over 12 | colds symptoms of upper respiratory tract with persisting mucus |
| 100-200 mg 3 times a day = 300-600 mg (gastro-resistant) | adults and adolescents over 12 | colds symptoms of upper respiratory tract with persisting mucus |
| 150 mg 3 times a day = 450 mg | adults and adolescents over 12 | colds symptoms of upper respiratory tract with persisting mucus |
| **since 1996** | | |
| Soft capsules (oral administration) | | |
| 200 mg 3 times a day = 600 mg | adults and adolescents over 12 | colds symptoms of upper respiratory tract with persisting mucus |
| **since 1997** | | |
| **soft capsule** (oral administration) | | |
| 200 mg 3 times a day= 600 mg (gastro-resistant) | adults and adolescents over 12 | colds symptoms of upper respiratory tract with persisting mucus |

| | | |
|---|---|---|
| 200 mg 3 times a day= 600 mg (gastro-resistant) | adults and adolescents over 12 | colds symptoms of upper respiratory tract with persisting mucus |

[#] 10 – 30 ml bath additives/100 l water: 1.46 g-2.57 g pure Eucalyptus oil in 10 ml bath additive; bath 35-38°C for 10 – 20 minutes; 3-4 times a week

[##] Ointments are typically packed in tubes with an opening of about 0.5 cm; that means 2-3 cm are approximately 0.4-0.6 ml and 6 cm are 1.2 ml; the average density of the ointments is 0.92 g/ml; that means the single doses for this ointments range from 0.04–0.11 g Eucalyptus oil.

*** 30 years tradition according data for historical and current medicinal products in addition (more than one product)

****30 years tradition according data for historical and current medicinal products in addition (more than one product) including German Standardzulassung 1996-2013

## Regulatory status overview

| Member State | Regulatory Status | | | | Comments |
|---|---|---|---|---|---|
| Austria | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products |
| Belgium | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | combination |
| Bulgaria | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Cyprus | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products |
| Czech Republic | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Denmark | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products |
| Estonia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | combination |
| Finland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products |
| France | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | No products |
| Germany | ☒ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | and in combination |
| Greece | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Hungary | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Iceland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Ireland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Italy | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | food supplement |
| Latvia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | combination, food supplement |
| Liechtenstein | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Lithuania | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Luxemburg | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Malta | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| The Netherlands | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Norway | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Poland | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Portugal | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Romania | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Serbia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | food supplement |
| Slovak Republic | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | combination |
| Slovenia | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |
| Spain | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | combination |
| Sweden | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | combination |
| United Kingdom | ☐ MA | ☐ TRAD | ☐ Other TRAD | ☐ Other Specify: | |

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'

This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

### 1.3. Search and assessment methodology

Data bases PubMed (April 2011) and DIMDI – DB (Deutsche Institut für medizinische Dokumentation und Information, XMESALL, XMEDCORE, XTOXLIALL, XTOXLICORE) were searched using the terms: "*Eucalyptus* oil, *Eucalyptus* leaves, *Eucalyptus globulus*, *Eucalyptus smithii, Eucalyptus polybractea, Euclayptus fructiceorum*, Cineole". Additional handbooks and textbooks as cited in the List of references were used.

Only articles found to be relevant for assessment are included in the List of references.

## 2. Historical data on medicinal use

### 2.1. Information on period of medicinal use in the Community

Beside the described well-established use of Eucalyptus oil containing products (see section 1.2), the usage of Eucalyptus oil has a long history and the importance is underlined by the release of a standard license in Germany [German Standardzulassung Eucalyptusöl Nr. 6599.99.99 1996]. Furthermore, a traditional use can be regarded as demonstrated because monographs on Eucalyptus oil are included in many handbooks and in the national pharmacopoeias of the European Union (EU) Member States (see sections 2.2 and 2.3).

Already in 1873, Köhler described the use in South Europe and the benefits on health of Eucalyptus preparations. As an example, he described effects on fever, neuralgic pain, asthma, lung tuberculosis, and the use as an antiseptic agent [Köhler 1873].

In 1938, Madaus described the use of Eucalyptus oil as follows: "The oil stimulates the excretion of saliva and gastric juice. It enhances the appetite. Additionally it is used as an inhalation for the treatment of catarrh and inflammatory diseases of respiratory tract and in cases of asthma. It is also used as a remedy for fever, catarrh of the urinary tract, influenza, rheumatism, neuralgias, malaria, fevered diarrhoea, gum bleeding and as an anthelmintic. Beside an oral application of Eucalyptus oil, topical use as an antiseptic agent, repellent, and for the treatment of arthritis and articular pain, have been reported" [Madaus 1938].

A survey, filled in by parents of children and adolescents, was conducted in Germany in 2007. Its results showed that 43.9% of the children had been given Eucalyptus preparations in the past 6 years [Hümer *et al.* 2010]. No further information about the applied products or their indication was given. However it confirmed the use and the tradition of Eucalyptus in the EU as a medicinal product.

### 2.2. Information on traditional/current indications and specified substances/preparations

In folk medicine, it is used internally for the treatment of asthma, fever, flu, whooping cough, loss of appetite, dyspeptic complaints, inflammatory and infectious diseases of kidneys and bladder, diabetes, rheumatic complaints. It is used externally for wounds, acne, poorly healing ulcers, stomatitis, bleeding gums, rheumatism, neuralgia, gonorrhoea. All these applications have not been confirmed scientifically by clinical studies [Blaschek *et al*. 2007].

The monograph of the Commission E approves the internal and topical use of Eucalyptus oil for catarrhs of the respiratory tract and its external use for rheumatic complaints [Blumenthal *et al*. 1998].

The German Standardzulassung “Eucalyptusöl” describes the internal and external (topical and inhalant) use for the treatment of diseases of the upper respiratory tract and the external use for the treatment of rheumatic complaints [German Standardzulassung Eucalyptusöl Nr. 6599.99.99 1996].

The Pharmacopée Française [1978] monograph “Huile essentielle d’Eucalyptus” described mucolytic and antiseptic effects (oral, inhalant).

Diepenbrock’s Gehes Codes [1960] reports on the use of Eucalyptus oil (prepared from only *E. globulus*) for the treatment of disorders of respiratory tract, bronchial catarrh and stomach pain.

Reynolds *et al.* [1989] listed Eucalyptus oil as a product that has been taken orally for catarrh and topically as a rubefacient. In a more recent edition of The Martindale [Sweetman 2007], it has been referred: “Eucalyptus oil has been taken by mouth for catarrh and coughs and is an ingredient of a lot of preparations. It has been used as an inhalant, often in combination with other volatile oils substances. Eucalyptus oil has also been applied as a rubefacient and is used as a flavour agent. It is also used in aromatherapy.”

The ESCOP monograph [2003] listed the following therapeutic indications for Eucalyptus oil: “Internal use: adjuvant treatment of chronic obstructive respiratory complaints including bronchitis and bronchial asthma; symptomatic relief of colds and catarrh of the upper respiratory tract. External use: symptomatic treatment of colds and rheumatic complaints.”

The British Herbal Compendium [Bradley 2006] refers to the ESCOP monograph.

The WHO monograph [2002] referred to the Commission E monograph and to The Martindale [Reynolds *et al.* 1996]. According to these, Eucalyptus oil is used for symptomatic treatment of catarrh and coughs, and as a component of certain dental root canal sealers; topically as a rubefacient for treatment of rheumatic complaints. Uses described in folk medicine, not supported by experimental or clinical data, include treatment of cystitis, diabetes, gastritis, kidney disease (unspecified), neuralgia, laryngitis, leucorrhoea, malaria, pimples, ringworm, sinusitis, wounds, ulcers of the skin, urethritis and vaginitis [WHO monographs 2002].

Traditional use outside the EU

In Australia, Brazil and South Africa, the use of Eucalyptus for the treatment of different kinds of complaints e.g. malaria, cancer, colds and rheumatism have been reported [Madaus 1938]. None of these indications are supported by scientific data.

The original inhabitants of Australia, the aboriginal people, already took advantage of the medicinal benefits of Eucalyptus oil [Sherry *et al.* 2001].

An inquiry of 100 adults yielded that, in Oregon (USA), Eucalyptus and its preparations was used for the treatment of cough, colds, sore throat and sinusitis. Thirty-nine percent of the interviewed persons stated the use of Eucalyptus and 89.7% confirmed effectiveness [Brown and Marcy 1991].

A retrospective review showed that Eucalyptus preparations including Eucalyptus oil have been used by about 12% of asthmatic patients in USA and Mexico border population [Rivera *et al.* 2004]. Eucalyptus oil is approved by the FDA for food use (EAFUS -Everything Added to Food in the United States- list No 2081) [FDA 2013].

*Summary*:

*In conclusion, the oral use, inhalation and cutaneous use of Eucalyptus oil for the treatment of disorders of upper respiratory tract and colds and for the treatment of rheumatic complaints have been well described for a long time.*

*Handbooks, Gehes Codes and Pharmacopée Française as well as the existence in the EU of products marketed (some for more than 15 years, some for more than 30 years) provide evidence of the long-standing, medicinal use of Eucalyptus oil for at least 30 years. Traditional use for the treatment of several indications has been reported. Some of the cited therapeutic indications are insufficiently described and supported by scientific data, thus it is recommended to accept in the monograph only the indications which are appropriate for traditional use without the supervision of a medical practitioner for diagnostic purposes, prescription or monitoring of treatment. Because bronchial asthma and rheumatic complaints should be supervised by a medical practitioner, they are not included as traditional indications. However the traditional use of Eucalyptus oil when applied topically as a rubefacient can be verbalized in accordance with other traditional indications of essential oils as follows: "Traditional herbal medicinal product for the symptomatic relief of localised muscle pain". This is in compliance with other decisions of the HMPC (e.g. Menthae piperitae aetheroleum).*

*Based on the indications found in European handbooks and monographs, for which exist a sufficiently documented posology (see section 2.3), the following indications are accepted for traditional use without the supervision of a medical practitioner for diagnostic purposes, prescription or monitoring of treatment:*

*Oral use, cutaneous use, inhalation, use as bath additive:*
*"Traditionally used for relief of cough associated with cold."*

*Cutaneous use, use as bath additive:*
*"Traditional herbal medicinal product for the symptomatic relief of localised muscle pain."*

*These indications are not supported by sufficient pharmacological and clinical data (see section 4) to consider a well-established use for Eucalyptus oil.*

## *2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications*

The monograph of the Commission E on Eucalyptus oil in herbal medicinal products [Blumenthal *et al*. 1998] gives a daily dose for oral use of 0.3 to 0.6 g essential oil. For external use: several drops of the essential oil rubbed onto the skin (this may be diluted at 30 ml essential oil to 500 ml of a suitable carrier such as vegetable oil). As an ointment: semi-solid preparation containing 5-20% essential oil (in a base of paraffin, petroleum jelly or vegetable oil) for local application. The monograph also describes:
- a tincture, an aqueous-alcoholic preparation containing 5-10% essential oil for local application;
- the inhalation use: a few drops of essential oil added to hot water or to a vaporizer; deep inhalation of the steam vapour.

The ESCOP monograph on Eucalyptus oil 2003 gives the following posology:
- Internal use: 0.05-0.2 ml per dose, 0.3-0.6 ml daily dose; in capsules 100-200 mg, 2-5 times daily [Bradley 2006].- External use: for inhalation: 12 drops per 150 ml boiling water or a 1.5% (V/V) solution prepared from 15 ml per litre of warm water, treatment may be repeated up to 3 times daily. As a liniment containing 25% (V/V) of oil and as an ointment containing 1.3% (V/m), for adults and children over 12 years, to be applied as a thick layer, up to 3 times daily. As a lozenge: 0.2-15.0 mg dissolved slowly in the mouth, repeated every 0.5-1 hours. As a mouthwash containing 0.91 mg/ml: 20 ml as a gargle twice daily.

The British Herbal Compendium refers to the ESCOP monograph [Bradley 2006].

The standard license in Germany recommends, for the treatment of diseases of the respiratory tract, the traditional daily posology of: 3-4 drops oil orally, on sugar or in water, 3 times a day, 3-4 drops in hot water for inhalation and, for the topical use, some drops of the undiluted oil on the chest or back; for the treatment or rheumatic complaints: some drops on the affected areas of the skin [German Standardzulassung Eucalyptusöl Nr. 6599.99.99 1996].

The Pharmacopée Française [1978] monograph "Huile essentielle d'Eucalyptus" gives the following posology: oral use: capsules 0.1-0.2 g 2-5 times a day, 2-4 spoons of syrup 0.025 g /100 ml: adults take daily, inhalant: 15 drops in 150 ml water, nasal drops 0.002-0.005% solution in oil, suppository 0.12 g 1-2 times a day only adults, injection intramuscular or subcutaneous: adults take 0.25 g daily. External use as an antiseptic: 3% alcoholic solution or 2% ointment.

Schmid *et al.* [1979] summarised the common posologies for Eucalyptus leaf preparations and Eucalyptus oil. For Eucalyptus oil, they gave a common single dose of 0.2 g orally, 20% topically and for intramuscular injection a dose of 0.2 g (10% in oil) without further information. A later edition of their book restricted the oral dose as follows: 10 drops for adults and 4-6 drops for children between 2 and16 years of age (with the instruction not to apply to the face) [Braun *et al.* 2011].

*Summary:*

*Posology*

*Reported dosages vary considerably. Oral administration ranged from 0.05-0.2 ml or 100-200 mg oil (2-5 times a day). For topical use single dose ranged from a few drops of undiluted Eucalyptus oil to 2-6 cm string of Eucalyptus oil containing semi-solid dosage forms (2-4 times a day). Inhalant ranged from a few drops up to 15 drops in 150 ml boiling water (3 times a day). According to the decision of MLWP a single dose for inhalant is limited up to 3-8 drops per 250 ml boiling water for adults and adolescents; and up to 2-4 drops per 250 ml boiling water for children between 4 and 12 years of age.*

*The posology for bath additives is limited to 1.5-6 g oil/100 l water for adults and adolescents; and 0.5-3 ml oil /100 l water for children between 4 and 12 years of age.*

*Duration of use*

*Sufficient information on the duration of use is missing (information about the duration of use of the products on the German market varies from several days to 1 week or "not limited"), therefore the duration is limited to 1 week in accordance with the other monographs concerning the treatment of symptoms of cold including cough. The duration of use for the treatment of muscle pain is limited to 1 week for the use as bath additive and 2 weeks for cutaneous use.*

*Target populations*

*Only rare information on the patient group is available. Topical application is limited by ESCOP to adolescents over 12 years. The oral administration is limited for oral liquids by Schmid et al. for children between 2 years and 12 years & adolescents (4-6 drops) and adults (10 drops) and for semi-solid dosage forms there are distinct posologies for children between 2 and 12 years and adolescents over 12 years. Authorised oral products on the German market are only intended for the use in adults and adolescents over 12 years; only some bath additives for the treatment of symptoms of cold are also intended for the use in children between 2 and 12 years. Since there are no sufficient clinical data on children, the oral use should be restricted to adolescents over 12 years of age and the cutaneous use should be limited to children over 4 years of age. See section 5 of this assessment report.*

*No sufficient information is available for the applied amounts of tincture, nasal drops, syrup or liniment. Therefore, these dosage forms are not described in the monograph.*

*Information on posology related to uses not accepted in the monograph*
*For subcutaneous or intramuscular injections, a single dose of 0.2 g and a daily dose of 0.25 g has been reported for adults only. Since traditional herbal medicinal products are only for oral, external or/and inhalation preparations according to Article 16a of Directive 2001/83 EC, products intended for administration by injection have not been included in the monograph.*

# 3. Non-Clinical Data

## *3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof*

Eucalyptus oil is used as an antiseptic, antispasmodic stimulant agent in bronchitis, asthma and minor respiratory complaints. Externally used, it has increasing effects on blood flow and skin temperature. Therefore, it has been used in semi-solid dosage forms for the treatment of cough, to promote scar formation in burns and injuries and as an antirheumatic agent. Used as an inhalant 1,8-cineole it is well known that causes a sensation of cold and this is accompanied with a facilitated respiration [Saller et al. 1988]. *Thus* it is often inhaled in asthma, pharyngitis and related conditions [De Smet *et al.* 1992].

**Primary pharmacology**

**Antimicrobial activity**

Eucalyptus oil

Several studies concerning antimicrobial activity of Eucalyptus oil were conducted. While in some studies [Pattnaik *et al.* 1996, Bosnic *et al.* 2006] broad activity against several microbial strains were reported, other studies revealed no or only slight activity [Dellacassa and Menendez 1989, Harkenthal *et al.* 1999, Chung *et al.* 2007, Hendry *et al*. 2009]. In comparison crude Eucalyptus oil seems to be more efficacious against microorganisms grown in suspensions and biofilms compared with pure 1,8-cineole [Bosnic *et al.* 2006, Hendry *et al.* 2009, see table 2].

Table 1: Results of antibacterial testing (broth dilution method) in µg Eucalyptus oil/ml

| | Bosnic *et al.* 2006 | Pattnaik *et al.* 1996 | Harkenthal *et al.* 1999 [in %(V/V)] =~ 10 µl/ml | Hendry *et al.* 2009 |
|---|---|---|---|---|
| Gram-negative bacteria | | | | |
| *Citrobacter* sp.. | n.t. | MIC = 3.33 | MIC = 1.0%<br>MBC = 1.0% | n.t. |
| *Enterobacter aerogenes* | n.t. | n.t. | MIC = 2.0%<br>MBC = 2.0% | n.t. |
| *Escherichia coli* | MIC = 390<br>MBC = 390 | MIC = 1.66 | MIC = >4.0%<br>MBC = >4.0% | MIC = 8 000<br>MBC = 8 000 |
| *Klebsiella* spec. | n.t. | MIC = 3.33 | MIC = 0.5%<br>MBC = 0.5% | n.t. |
| *Salmonella sp.* | n.t. | MIC =1.66-3.33 (different species) | MIC = ~20 000<br>MBC = >~20 000 | n.t. |
| *Shigella flexneri* | n.t. | MIC = 0.88 | MIC = 0.25%<br>MBC = 0.25% | n.t. |

| | | | | |
|---|---|---|---|---|
| *Proteus mirabilis* | n.t. | n.t. | MIC = 2.0%<br>MBC = 2.0% | n.t. |
| *Pseudomonas aeruginosa* | MIC = 390<br>MBC = 390 | MIC = 8.33-20<br>(different strains) | MIC = > 4.0%<br>MBC = > 4.0% | MIC = 256 000<br>MBC = 256 000 |
| *Vibrio cholerae* | n.t. | MIC = 0.16-0.80<br>(different strains) | n.t. | n.t. |
| Gram-positive bacteria | | | | |
| *Bacillus brevis* | n.t. | MIC = 0.41 | n.t. | n.t. |
| *Bacillus circulans* | n.t. | MIC = 0.41 | n.t. | n.t. |
| *Bacillus subtilis* | MIC = 390<br>MBC = 12500 | n.t. | n.t. | n.t. |
| *Staphylococcus aureus* | MIC = 390<br>MBC = 3215 | MIC = 0.41 | n.t. | MIC = 4 000<br>MBC = 8 000 |
| *Staphylococcus aureus* (methicillin-resistant; MRSA) | n.t. | n.t. | n.t. | MIC = 2 000<br>MBC = 2 000 |

MIC = Minimal inhibition concentration; MBC = Minimal bactericidal concentration; n.t. = not tested

The results of Dellacassa &Menendez [1989] showed that there is no direct relation between the 1,8-cineole content and the inhibition zones observed for different oil derived from different *Eucalyptus* species including *E. globulus* (oil from *E. smithii* or *E. polybractea* has not been tested).

Also, results of Prabuseenivasan *et al.* [2006] antibacterial studies using the disc diffusion method, showed that Eucalyptus oil at different concentrations (50 µl diluted 1:1, 1:5, 1:10 and 1:20) against Gram-negative bacteria such as *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus vulgaris* and Gram-positive bacteria such as *Bacillus subtilis* and *Staphylococcus aureus* failed to inhibit the growth of any tested strains in contrast to 19 other oils such as Cinnamon oil or Lime oil.

Cermelli *et al.* 2008 investigated the antibacterial activity of *Eucalyptus globulus* essential oil on *Streptococcus pyogenes, S. pneumoniae, S. agalactiae, S. aureus, Haemophilis influenzae, Parainfluenzae* and *Stenotrophomonas maltophilia* as the most important causes of respiratory tract infections. Minimum inhibitory concentration (MIC) and minimum bacteriocidal concentration (MBC) ranged from 1.25 µl /ml to 50 µl /ml (~1.25-50 mg/ml).

1,8-Cineole

Bosnic *et al.* [2006] showed, that 1,8-cineole (unknown concentration) was active against two Gram-positive bacteria (*S. aureus*, *B. subtilis*), while it was inactiveagainst the Gram-negative bacteria *E. coli* and *P. aeruginosa*). Whereas Hendry *et al.* [2009] also showed a positive effect against *E. coli* [see table 2].

Table 2: Results of antibacterial testing (microbroth dilution method) of 1,8 cineole [Hendry *et al.* 2009]

| | **MIC** | **MBC** |
|---|---|---|
| Gram-negative bacteria | | |
| *Escherichia coli* | 64 mg/ml | 64 mg/ml |
| *Pseudomonas aeruginosa* | >256 mg/ml | >256 mg/ml |
| Gram-positive bacteria | | |
| *Staphylococcus aureus* | 16 mg/ml | 256 mg/ml |
| *Staphylococcus aureus* (methicillin-resistant; MRSA) | 64 mg/ml | 256 mg/ml |

MIC = Minimal inhibition concentration; MBC = Minimal bactericidal concentration

**Antifungal activity**

Eucalyptus oil

Pattnaik *et al.* [1996] tested Eucalyptus oil against twelve fungi (yeast-like and filamentous). MICs between 0.025 and 1% (V/V) were found. Agarwal *et al.* [2008] tested 30 plant oils for anti-*Candida* activity against two different strains of *Candida albicans.* A concentration of 0.05% (V/V) was enough to inhibit growth completely, while Hendry *et al*. [2009] give MIC value of 2-8 mg/ml. Antifungal effects of Eucalyptus oil were also observed against five *Fusarium* species [Rai *et al*. 1999].

Table 2: Results of antifungal testing (broth dilution method) in µl/ml

| | Pattnaik *et al.* 1996 (agar dilution assay) | Agarwal *et al.* 2008 (agar dilution assay) | Hendry *et al.* 2009 |
|---|---|---|---|
| *Alternaria citrii* | MIC = 0.75 | n.t. | n.t. |
| *Aspergillus fumigatus* | MIC = 1.5 | n.t. | n.t. |
| *Aspergillus oryzae* | MIC = 1.0 | n.t. | n.t. |
| *Candida albicans*. | MIC = 5.0 | MIC = ~0.5 | MIC = ~2.0/8.0 (duplicate) |
| *Cryptococcus neoformans* | MIC = 5.0 | n.t. | n.t. |
| *Fusarium oxysporum* | MIC = 2.0 | n.t. | n.t. |
| *Fusarium* spec. | MIC = 5.0 | n.t. | n.t. |
| *Helminthosporum compactum* | MIC = 10.0 | n.t. | n.t. |
| *Macrophomina phaseolina* | MIC = 2.0 | n.t. | n.t. |
| *Sclerotium rolfsii* | MIC = 0.5 | n.t. | n.t. |
| *Sporothrix schenkii* | MIC = 5.0 | n.t. | n.t. |
| *Trichophyton mentagrophytes* | MIC = 0.25 | n.t. | n.t. |

MIC = Minimal inhibition concentration; n.t. = not tested

1,8-Cineole

Hendry *et al.* [2009] tested 1,8-cineole against *Candida albicans*. The MIC value was 2-8 mg/ml, while the MBC was 64 mg/ml (microbroth dilution method).

**Antiviral activity**

Eucalyptus oil

The potential antiviral effect of Eucalyptus oil was determined against *Herpes simplex* virus type I (HSV-1) *in-vitro* by Astani *et al.* [2010]. HSV-1 was incubated with various concentrations of Eucalyptus oil for one hour at room temperature. The $IC_{50}$ could be given with 55 µg/ml. At maximum non-cytotoxic concentration (200 µg/ml = ~0.02%) plaque formation was significantly reduced 3 days after cell infection by >96% after pre-incubation of HSV-1 and essential oil compared with untreated control. Only moderate activity was seen when the essential oil was added to host cells prior or after infection. Also Schnitzler *et al.* 2001 demonstrated that Eucalyptus oil (0.01%) reduced virus titers by 58-75% for HSV-1 and HSV-2. It could be shown that pre-treatment of virus with the essential oil showed best results while pre-incubation of the cells did not reduce virus production.

Cermelli *et al.* 2008 investigated the antiviral activity of *Eucalyptus globulus* essential oil on strains of adenovirus and mumps virus isolated from patients. In a concentration of 0.25 µl/ml (0.025%) the essential oil showed a mild antiviral activity (~40%) against mumps virus, but nor against adenovirus.

1,8-Cineole

The potential antiviral effect of 1,8-cineole was determined against *Herpes simplex* virus type I (HSV-1) *in-vitro* by Astani *et al.* [2010]. The $IC_{50}$ could be given with 1200 µg/ml.

α-Pinene

The potential antiviral effect of α-pinene was determined against *Herpes simplex* virus type I (HSV-1) *in-vitro* by Astani *et al.* [2010]. The $IC_{50}$ could be given with 4.5 µg/ml.

**Influence on respiratory tract fluid/ciliary beat frequency**

Eucalyptus oil

*in-vivo*-studies:
In 1946 Boyd and Pearson tested the expectorant properties of Eucalyptus oil to guinea pigs in doses of 10, 50 and 100 mg/kg body weight given by stomach tube. A concentration of 50 mg/kg (Human Equivalent Dose (HED) = 11 mg/kg) has been found to be maximal effective in augmenting the output of respiratory tract fluid (RTF). An increasing effect on the output of RTF could also be found in dogs, cats, rabbits and albino rats. The average recommended dose in man was reported with 10 mg essential oil/kg body weight.

Boyd and Sheppard [1968] studied the effect of steam inhalation of Eucalyptus oil on the output of RTF in urethane treated rabbits. The administration of Eucalyptus oil by inhalation added only little to the output of RTF in doses caused death (19.683 mg/kg). But lower doses had no effect on the volume of RTF.

*in-vitro*-studies:
Effects of different essential oils on the activity of ciliated epithelial brushings of inferior nasal turbinate have been examined *ex-vivo* in order to estimate benefits of alternative treatments of bronchitis and rhinitis. Brushings of inferior nasal turbinate were placed on slides and exposed to 2, 5, 10 and 20 min with Eucalyptus oil. An increase in ciliary beat frequency of 20% at 10 min exposure with 0.2% eucalyptus oil (~2,000 µg/ml) and remained elevated at 20 min has been observed. 2% eucalyptus oil (~20,000 µg/ml) resulted in an increase of ciliary beat frequency of 11.8% at 5 min [Neher *et al.* 2008].

When investigating a possible side effect of inhaled essential oils on the activity of nasal respiratory cells, Riechelmann *et al.* [1997] found that Eucalyptus oil exposed in a concentration above 6.7 $g/m^3$ can also reduce *in-vitro* ciliary activity of human respiratory cells. But according to the authors' opinion, inhalative concentrations of essential oils exceeding 5 $g/m^3$ will not be achieved when cold remedies containing essential oils are used at recommended posologies, but can occur, when overdosed.

Zänker *et al*. [1980] investigated the effect of vapours of Eucalyptus oil on synthetic and pulmonary surfactant layers. Under their experimental conditions, Eucalyptus oil exhibited surfactant-like effects, namely a decrease in surface tension between water and air.

1,8-cineole

*in-vivo* studies:
Laude *et al.* [1994] studied the antitussive effects of 1,8-cineole in conscious guinea-pigs. 1,8-cineole (0.8, 2.7 and 8 µg/ml) administered by using a vaporising apparatus that provided a constant airflow of 1 ml/min. Cough was induced by citric acid (initial dose 300 mM/24 h). Results showed that 1,8-cineole had no significant effect on cough frequency.

During inhalation of 300 µmol 1,8-cineole the lung compliance of anaesthetised rabbits was improved by a factor 0.3. An increase of 1,8-cineole posology resulted in a decrease of lung compliance

compared to starting values. No remarkable morphological damage of epithelium has been observed [Zänker *et al*. 1980].

*in-vitro* studies:
Zänker *et al*. [1980] investigated the effect of vapours of 1,8-cineole on synthetic and pulmonary surfactant layers. Under their experimental conditions, 1,8-cineole exhibited surfactant-like effects, namely a decrease in surface tension between water and air and thus improved lung compliance values *in-vitro*.

**Anti-inflammatory activities**

Eucalyptus oil

*in-vivo* studies:
Silva *et al.* [2003] demonstrated an anti-inflammatory effect of Eucalyptus oil in the paw oedema test in rats after subcutaneous injection in a dosage of 100 mg/kg (HED = 16 mg/kg).

Serafino *et al.* [2008] administered Eucalyptus oil to rats p.o. in a dosage of 12 mg/kg/day for 15 days (HED = 1.9 mg/kg) to test whether Eucalyptus oil treatment could induce a recovery of peripheral blood mononuclear cells activity after bone marrow suppression (by 5-fluorouracil on day 7). In the sets of experiment, blood was collected on day 0, 7, 15 and 20. At day 15, an increase of circulating monocytes and an increment in the phagocytic activity of granulocytes and monocytes were recorded for immuno-competent rats. In immuno-supressed rats, a recovery of the percentage of circulating granulocytes was observed as well as an nearly restored phagocytic activity of peripheral blood granulocytes/monocytes.

*in-vitro*-studies:
Data from Serafino *et al.* [2008] demonstrated that Eucalyptus oil (~73 and 146 µg/ml) increased the phagocytic activity of human monocyte derived macrophages after 24 h treatment, while the release of immune-modulating cytokines (IL-2, IL-4, IL-6, IL-10, TNF-$\alpha$, INF-$\gamma$) was not influenced.

In order to prove the ability to reduce cytokine release, Rantzsch *et al.* [2009] confirmed an anti-inflammatory effect of Eucalyptus oil in *ex-vivo* cultured and stimulated alveolar macrophages from patients with chronic obstructive pulmonary disease (COPD). Reduction of TNF-$\alpha$ release from LPS-stimulated macrophages was observed with ~1 µg Eucalyptus oil/ml.

1,8-Cineole

*in-vivo* studies:
Patients and healthy subjects were given 3 x 200 mg 1.8-cineole per day for 3 days, blood samples were taken and monocytes isolated. Production of $LTB_4$ and $PGE_2$, both metabolites of the arachidonic acid pathways, from isolated blood monocytes, which were stimulated with A23187 *ex-vivo* was studied. Spontaneous $LTB_4$ and $PGE_2$-production in patients with treated bronchial asthma was lower than in healthy volunteers. After 3 days of treatment, $LTB_4$ and $PGE_2$-production in isolated, activated blood monocytes were significantly suppressed in both groups. It was postulated that 1,8-cineole reveals a useful anti-inflammatory activity profile [Juergens *et al*. 1998a].

An inhibition of cytokine production *in-vitro* by 1,8-cineole has also been found. Cell cultures of lymphocytes and monocytes from 9 volunteers, who donated their venous blood, were stimulated and treated with 1,8-cineole ($10^{-9}$-$10^{-5}$ M) [Juergens *et al*. 2004]. Inhibitory effects on IL-1β, TNF-$\alpha$, IL-4, IL-5 and IL-8 could be found in physiologic achievable concentrations ($10^{-5}$ M).

Santos and Rao [2000] investigated the influence of 1,8-cineole (oral administration) in rats on inflammatory events (carrageenan-induced hind paw oedema, cotton pellet-induced granuloma). A dose of 400 mg/kg (HED = 64.5 mg/kg) provoked clear inhibition of the experimental inflammations.

*in-vitro* studies:
Venous blood from healthy donors was taken and the monocytes were isolated and incubated with 1,8-cineole (0.1-1,000 ng/ml) for 20 h in the presence of LPS or IL-1β. LPS-stimulated monocytic production of the representative arachidonic acid metabolites $LTB_4$ and $TxB_2$ and of IL-1β were inhibited (1,000 ng/ml). LPS and IL-1β-stimulated production of TNF-α was also inhibited [Juergens *et al*. 1998b].

**Analgesic / antinociceptive activity**

Eucalyptus oil

*in-vivo* studies:
Silva *et al.* [2003] showed that Eucalyptus oil induced analgesic effects. Analgesic effect was demonstrated by i.p. injection at doses of 10 or 100 mg/kg (rats, positive control: morphine; HED = 1.6 and 16 mg/kg) and by subcutaneous injection at doses of 0.1, 10 and 100 mg/kg (acetic acid-induced writhing mice; HED = 0.16, 1.6 and 16 mg/kg).

1,8-Cineole

*in-vivo* studies:
Santos and Rao [2000] investigated the effect of 1,8-cineole (oral administration) in mice on chemical (acetic acid and formalin) nociception. In the formalin test, a dosage of 400 mg/kg (HED = 32.5 mg/kg) inhibited significantly the paw licking response while a dosage of 200 mg/kg (HED = 16.2 mg/kg) inhibited only the second phase. The incidence of abdominal constriction response was found to be significantly less even in the lowest dose of 100 mg/kg (HED = 8.1 mg/kg).

Antinociceptive effects of 1,8-cineole was examined in rats and mice (tail-flick, hot plate). A dosage of 0.3 mg 1,8-cineole/kg in rats (i.p.) provoked a significant effect on reaction time to nociceptive effects in rats, while changes in reaction in mice could not be seen [Liapi *et al*. 2007].

β-pinene

*in-vivo* studies:
Antinociceptive effects of β-pinene were examined in rats and mice (tail-flick, hot plate). β-pinene provoked a supraspinal antinociceptive action in rats only (0.3 mg/kg, i.p.) [Liapi *et al*. 2007].

**Secondary pharmacology**

**Antioxidant activities**

Antioxidant properties of essential oils are well known and have been confirmed by several studies [Dessi *et al.* 2001, Lee and Shibamoto 2001]. In order to prove the ability of essential oils to reduce reactive oxygen species (ROS) production Rantzsch *et al.* [2009] even confirmed an antioxidant effect of Eucalyptus oil (1 µg/ml) in *ex-vivo* cultured and stimulated alveolar macrophages from patients with chronic obstructive pulmonary disease (COPD). But the exact mechanism on how essential oils exert this function on inflammatory cells is still unknown. Whether this effect correlates with clinical measurable benefits for the patients has also to be studied.

**Other effects**

Antidiabetic effects [Faulds 1902] and repellent effects [Juan *et al.* 2011, Yang *et al.* 2004, Erler *et al.* 2006, Toloza *et al.* 2006, 2010] have been reported for Eucalyptus oil. But since these effects are not relevant to the traditional indications described above in sections 1 and 2, an overview of the available data concerning these effects is not given here.

**Safety pharmacology**

No information available.

**Pharmacodynamic interactions**

No information available.

*Summary*

*in-vitro studies:*
*Several studies on the effects on bacterial strains, viruses and fungi were conducted. While some authors found antibiotic activity of the essential oil in concentration that are likely to be achieved in the clinical situation, several other authors could find such an activity only in concentrations which are far above physiological possibility. Therefore, the antibiotic activity (especially because even decreased susceptibilities to Eucalyptus oil and 1,8-cineole were described) seems not to be supported by convincing non-clinical data. Also antifungal and antiviral effects of the essential oil were recognised in concentrations which are most likely to be too high to get achieved in clinical situations. This is also applicable for the tests concerning respiratory tract fluid/ciliary beat frequency. Effects connected to the phagocytic activity of macrophages seem to be more plausible.*

*in-vivo studies:*
*According to the data and as found in the monograph, use is recommended with a single dose up to 200 mg. For a 60 kg adult, this would mean 3.3 mg/kg. Most in-vivo effects were investigated only in concentrations above this (expectorant properties, anti-inflammatory effects). Effects on phagocytic activity could be seen in dosages of 1.9 mg/kg (HED), and analgesic effects occurred after i.p. and s.c. administration of even smaller amounts. These effects seem to possess some plausibility at least in reference to the dosages administered.*

*Also for 1,8-cineole, of the many results reported, some effects occurred only in concentrations too high to be clinical relevant. Worth mentioning are here the antitussive effects seen in conscious guinea-pigs by using a vaporising apparatus and the influence seen ex-vivo on monocytes of patients which were treated with 1,8-cineole, even though it is not clear if these results are transferrable to the essential oil.*

*Studies concerning safety pharmacology and pharmacodynamic interactions were not found.*

## *3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof*

Eucalyptus oil

Sufficient data on the metabolism of Eucalyptus oil are missing. Excretion of Eucalyptus oil appears to be complex. Lungs, kidneys, bowel and skin are involved [Darben *et al.* 1998].

Several studies showed an enhancing effect of Eucalyptus oil on skin penetration of drugs such as trazodone hydrochloride, chlorhexidine or 5-fluorouracil [Karpanen *et al.* 2010, Das *et al.* 2006, Abdullah *et al.* 1996]. This effect is worth noticing in case of concomitant topical application of other medicinal products.

Unger and Frank [2004] established an automated online extraction method (LC/LC/MS) in order to assess the *in-vitro* inhibitory potential of herbal extracts and oils on cytochrome P-450 system. Single enzymes and corresponding substrates were incubated with the test solutions (500, 100, 20 µg/ml). Corresponding metabolites were determined and quantified. Results for Eucalyptus oil indicate that it is only a weak inhibitor of CYP enzymes (available mixture of CYP1A2/2C8/2C9/2C19/2D6/3A4) with $IC_{50}$ values >100 µg/ml. Inhibition of CYP3A4 was a little bit stronger ($IC_{50}$ values 20-100 µg/ml) than the inhibition of the others. In comparison to Peppermint oil, Eucalyptus oil was a weaker inhibitor.

These findings correspond to the results obtained by Miyazawa *et al.* [2001b], who reported that 1,8-cineole is one of the effective substrates for CYP3A4 enzymes in rat and human liver microsomes.

1,8-cineole

As the main component of Eucalyptus oil is 1,8-cineole, data on the pharmacokinetic of 1,8-cineole are given below.

1,8-cineole is a lipophilic substance. It is rapidly absorbed through skin and mucosa. Oral and rectal administration or inhalation have also been described [Saller *et al.* 1988].

Weyers and Brodbeck [1989] applied a mixture of Pine oil, Eucalyptus oil, Arnica oil and rosemary on depilated rats skin in order to determine whether 1,8-cineole (as the active component) can be detected in effective amounts at the target area in skeletal muscles after dermal application. Relative bioavailability obtained by using an applicator (2 foam layers with an aluminium foil on the outside) was 320% as compared with that obtained by using an occlusive dressing. Since the applicator caused an increase of 5°C of body temperature, its use may result in a better absorption (resorption). A good percutaneous absorption (resorption) of 1,8-cineole from topically applied essential oils can be regarded as confirmed by these results.

Most studies on the pharmacokinetics of 1,8-cineole have been performed in brushtail possum. Brushtail possums are herbivores that feed on Eucalyptus leaves [McLean *et al*. 2007, Pass *et al*. 2001, Southwell and Flynn 1980]. Their detoxification capacity is higher than that of humans, therefore the results of these studies are not necessarily transferable to humans and thus they are not summarised in this assessment report. Pass *et al.* 2001 studied the metabolism of 1,8-cineole in brushtail possum, koala, rats and also in human (*ex-vivo*). After incubation of pooled human liver microsomes with 1,8-cineole three metabolites were detected: 2-hydroxycineole (72%), trace amounts of 9-hydroxycineole (8.9%) and one unknown hydroxyl-cineole metabolite (19.2%). Miyazawa and Shindo [2001] investigated the biotransformation of 1,8-cineole in human liver microsomes. Only one metabolite, 2-exo-hydroxy-1,8-cineole, was found. Duisken *et al.* [2005] could confirm a biotransformation of 1,8-cineole by human liver microsomes to 2α-hydroxy-1,8-cineole and 3α-hydroxy-1,8-cineole and the excretion of these metabolites in urine of 84 volunteers after oral medication of 1,8-cineole, without further information about used posologies.

Several metabolites such as 1,8-dihydroxy-10-carboxy-p-menthane, 2-hydroxy-cineole and 3-hydroxy-cineole have been identified in rat urine after oral administration [Madyastha and Chadha 1986, De Vincenzi *et al*. 2002]. In rabbit urine, the same metabolites, 2- and 3-hydroxy-cineole have been identified [Miyazawa *et al.* 1989]. Hydroxycineole is excreted as its glucuronic acid [Opdyke 1975].

A maximum concentration of 1,8-cineole in rabbit plasma was found after 30 min and the concentration decreased slowly between 1 to 4 h. Maximum concentration of free metabolites (2-exo, 2-endo- and 3-exo-hydroxycineole) occurred after 1 h and decreased slowly after 2 h. The conjugated metabolites showed a maximum concentration after 1.5 to 2 h. Their concentration decreased 2-4 h after the administration [Miyazawa *et al.* 1989].

Effects of 1,8-cineole on the liver and lung enzyme system

1,8-cineole has been found to increase significantly the activity of the microsomal enzyme system (Jori *et al*. 1969). Rats were treated by subcutaneous injection (1,8-cineole 500 mg/kg daily for 4 days) or aerosol inhalation (4 days, twice 15 min and twice 30 min; 50 mg/min). *In-vitro* microsomal activities of O-demethylation of p-nitroanisol, 4-N-demethylation of aminoantipyrene and p-hydroxylation of aniline were significantly increased after 1,8-cineole administration. *In-vivo* effects were demonstrated on metabolism and pharmacological actions of pentobarbital (25-30 mg/kg i.p. 7, 18, 36 and 48 h after administration of 1,8-cineole). Administration of 1,8-cineole, s.c.or by aerosol inhalation, showed a

significant decrease in pentobarbital effect. The sleeping time and pentobarbital concentration in brain of treated rats were less than in the control group. Effects were dose-dependent and disappeared after 48 h (s.c.) and 72 h (after last inhalation). A follow-up study confirmed these results, but showed that the liver concentration of the cytochrome P-450 was not modified by 1,8-cineole administration [Jori *et al.* 1972].

The effect of 1,8-cineole on liver and lung microsomal cytochrome P-450 and $b_5$ systems of rats has been investigated by Madyastha and Chadha [1986]. They found that 1,8-cineole administered by inhalation induced liver microsomal cytochrome P-450 level after 3-9 days of treatment. The level of cytochrome $b_5$ showed only a slight increase. In contrast, the level in lung microsomes was not increased. The levels of NADPH and NAD cytochrome c reductase from both lung and liver microsomes seemed to be unaffected.

An inhibitory effect on 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG CoA reductase) could be shown by administration of 1,8-cineole to male Wistar rats (by a gastric tube 3 mmol/kg) [Clegg *et al*. 1980, 1982].

A dose-dependent increased activity of glucuronytranferase (GFA) in rats after administration of 1,8-cineole (inhalation 150 mg/min for 5-8 days or s.c. 500 and 1,000 mg/kg for 4 days) was found by Hohenwallner and Klima [1971].

Saify *et al.* [2000] investigated the skin penetration enhancer effect of 1,8-cineole towards 5-flurouracil into rats. 1,8-cineole was found to be very active, no lag time was observed, it caused an 83-fold increase in drug permeability. Due to their results, the authors assumed that enhanced penetration may not only be caused by an increased partition of the drug into stratum corneum, but also by modifying intercellular lipids. Disrupting their highly ordered structure, an increased diffusion of the drug through skin may occur.

*Summary:*

*Excretion of Eucalyptus oil appears to be very complex. Sufficient data on metabolism of Eucalyptus oil are missing while several studies indicate an enhancing effect on skin penetration. An inhibitory effect of Eucalyptus oil on cytochrome P-450 enzymes has been confirmed in-vitro and is plausible against the background of the in-vitro and in-vivo findings for 1,8-cineole after s.c. injection and aerosol inhalation. However, the tested concentrations used in these experimental studies are multiple higher than plasma levels achieved at the therapeutic human dose.*

*Skin absorption of terpenes has been demonstrated by Römmelt et al. [1974] for Pine needle and Spruce needle oil. Given their comparable and lipophilic structure, it is likely that the percutaneous absorption of 1,8-cineole is comparable to that of the terpenes tested by Römmelt et al. Weyers and Brodbeck [1989] confirmed that 1,8-cineole has been absorbed by skin and could be detected in effective amounts at the target area in skeletal muscles after dermal application. An additional absorption from breathing air by mucosa may contribute to the treatment of diseases of the upper respiratory tract. Terpenes such as 1,8-cineole, topically applied, lead to an improvement of circulation that probably contributes to pain reduction in muscular pain and joint problems.*

*Metabolism and excretion of 1,8-cineole have been investigated in animal and ex-vivo studies. The main metabolites of 1,8-cineole are hydroxylated forms which are excreted as its glucuronic acids.*

## *3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof*

Only rare non-clinical data are available on the toxicity of Eucalyptus oil. Therefore data on 1,8-cineole as the main constituent of the essential oil, are also cited.

**Acute toxicity**

Eucalyptus oil

Based on animal studies, the oral $LD_{50}$ for Eucalyptus oil is 4.4 g/kg b.w. for rats and 3.3 g/kg for mice [ESCOP 2003]. The $LD_{50}$ is lower for 1,8-cineole with 2.5 g/kg for rats [Opdyke 1975].

Information on toxicity of Eucalyptus oil has been reported as case studies after accidental ingestion or overdosing. See section 5.3.

1,8-cineole

The $LD_{50}$ oral dose on Osborne-Mendel rats of 2,480 mg/kg b.w. was found by Jenner *et al.* [1964].

De Vincenzi *et al*. [2002] summarised the toxicity data on 1,8-cineole. Toxicity studies reported in rats and mice suggested that mice were less susceptible than rats to the toxicity of 1,8-cineole. After gavage of 150 to 2,400 mg/kg/day, a dose-related reduction in the body weight gain and a histopathological damage of the liver in male rats were observed. The highest dose of 2,400 mg/kg/day showed 50% of mortality in both sexes. 1,8-cineole given in encapsulated form corresponding to 0, 381, 766, 1,740 and 3,342 mg/kg showed a dose-related histopathological alteration of liver, kidney and parotid gland at all dose levels only in male rats. Treatment of mice by gavage for 28 days at dose of 0, 150, 300, 600, 1,200 mg/kg/day, did not result in any dose-related lesions in either sex. After the treatment by encapsulated 1,8-cineole corresponding to 0, 600, 1,322, 2,448, 5,607 mg/kg/day, a minimal dose-related hypertrophy of centrilobular hepatocytes was observed. This supports the assumption that exposure to 1,8-cineole over the whole day induces a stronger response in the tissue than a single, short daily exposure.

Kristiansen and Madsen [1995] found that the treatment of Wistar rats with 1,8-cineole in food at doses of 500 and 1,000 mg/kg b.w. for 28 days can cause renal lesions. Body weight was decreased and relative liver and kidney weights were significantly increased in all groups, whereas the relative brain weight was increased only in the 1,000 mg/kg dosed group. Histopathological changes in the brain were not observed. Whether these findings are relevant for humans in traditional dosages has to be investigated.

The dermal $LD_{50}$ for rabbits is more than 5 g/kg 1,8-cineole b.w. [Opdyke 1975].

**Mutagenicity**

Eucalyptus oil

Miyamoto *et al.* [2009] evaluated the genotoxic potential of *Eucalyptus globulus* oil using a somatic segregation assay and the filamentous fungus *Aspergillus nidulans*. The results pointed to a genotoxicity of Eucalyptus oil (0.12 and 0.25 µl/ml showed an increase of mitotic recombinants of *A. nidulans*) but they also pointed to the need to assess the recombinogenic potential of the oil in mammalian cells.

1,8-Cineole

Gomes-Carneiro *et al*. [1998] tested the mutagenicity of 1,8-cineole at the dose of 250 µg/plate by the *Salmonella* reverse mutation assay with TA97a, TA98, TA100 and TA102 as tester strains. Positive and

negative controls were included. No mutagenic effect was found. However, it has to be noted that the bacterial strains used are not completely in accordance to the OECD Guideline No. 471.

Sasaki *et al*. [1989] treated Chinese hamster ovary cells with 0.15 µm mitomycin C for 21 h and post-treated them with 1,8-cineole at concentrations of 0, 3.3, 10, 33.3, 100, 333 (toxic) µM to investigate the effects on sister-chromatid exchange (SCE). Treatment with 1,8-cineole showed no influence on SCE induced by mitomycin C.

Horvathova *et al.* [2007] compared cytotoxic and DNA-damaging effects of 1,8-cineole on human leukemic K 562 cells to investigate a possible protective effect against hydrogen peroxide-induced DNA damage. 1,8-Cineole in a concentration of 2,000-5,000 µM showed neither DNA-damaging nor DNA-protective effects.

**Carcinogenicity**

No data on eucalyptus oil are available.

1,8-cineole

Stoner *et al*. [1973] examined the ability of 1,8-cineole to induce primary lung tumours. Mice received i.p. injections of 12.0 and 2.4 g/kg b.w. for 8 weeks and were killed at 24 weeks after first injection. Four mice out of 15 (dosage 12.0 g/kg) and 3 mice out of 15 (dosage 2.4 g/kg) developed a lung tumour during the study. But the authors pointed out that the pulmonary tumour response in mice should not be used as a sole index of carcinogenic activity of an agent.

The treatment of male Wistar rats with 1,8-cineole at doses of 500-1,000 mg/kg b.w. for 28 days can cause an accumulation of protein droplets containing α2µ-globulin in the proximal tubular epithelial cells [Kristiansen and Madson 1995]. On this basis, the authors concluded that 1,8-cineole belongs to the so-called CIGA carcinogens (chemical inducing α2-globulin accumulation). But it is important to recognise that α-2-microglobulins nephropathy is a phenomenon which is exclusively found in adult male rats. Since α-2-microglubulins do not occur in humans, a direct extrapolation of rats' data cannot be made [Swenberg *et al.* 1989].

*Assessor's comment:*
*A comparable concentration of 1,8-cineole cannot be reached by the administration of Eucalyptus oil according to the traditional posology. Therefore, these findings are not relevant for a traditional use.*

**Reproductive toxicology**

Eucalyptus oil

Experiments in mice did not show any embryotoxic or foetotoxic effects after subcutaneous administration of *Eucalyptus globulus* oil at 135 mg/kg body weight of pregnant mice on days 6 to 15 of gestation [ESCOP 2003; Pages *et al.* 1990].

*Assessor's comment:*
*A s.c. administration of Eucalyptus globulus oil like tested by Pages et al. 1990 is not intended for a traditional use.*

1,8-cineole

In order to investigate the possibility of stimulating drug metabolism in foetal and neonatal periods, pregnant and lactating rats were treated with 1,8-cineole (500 mg/kg s.c. daily for 4 days between day 10 and 14 of pregnancy or during the last 4 days of pregnancy or between day 2 and 6 after delivery). 1,8-cineole increased liver microsomal enzyme activity of mothers (for all experiments) and foetuses, but not in suckling newborn rats. Nursing mother rats, treated with 1,8-cineole, showed an increased

liver enzymatic activity, too. The authors concluded that 1,8-cineole cannot cross the blood-milk barrier, but it is able to penetrate the placenta tissue [Jori and Briatico 1973].

*Summary:*

*Based on animal studies, the oral $LD_{50}$ for Eucalyptus oil is 4.4 g/kg b.w. for rats and 3.3 g/kg for mice [ESCOP 2003]. Data on acute toxicity of Eucalyptus oil to humans are missing.*

*Tests on mutagenicity, carcinogenicity and reproductive toxicity are incomplete. Investigations on genotoxicity of Eucalyptus oil on Aspergillus nidulans pointed to an increase of mitotic recombinants. Test on human leukemic K 562 cells showed neither DNA-damaging nor DNA-protective effects of 1,8-cineole. No relevant data on the carcinogenicity of Eucalyptus oil or 1,8-cinoele are available. Tests concerning reproductive toxicity are not sufficient. Investigations on pregnant and lactating rats showed that 1,8-cineole cannot cross the blood-milk barrier, but is able to penetrate the placenta tissue.*

## *3.4. Overall conclusions on non-clinical data*

Pharmacodynamic:

Experimental pharmacological data point to some activity concerning phagocytic activity of monocytes and analgesic effects after i.p. and s.c. application even tough that this way of administration is not the intended route of application for traditional medicine. Further results often to be found in literature concern antimicrobial activity, anti-inflammatory and analgesic activity, influence on ciliary beat frequency of nasal respiratory cells, increase of the output of respiratory tract fluid in animals and anti-nociceptive activity. However, high doses of Eucalyptus oil were used to obtain those pharmacological effects. These doses mostly cannot be extrapolated to human conditions. Therefore, it cannot be proven that the relevant concentrations can be reached clinically. A benefit of pharmaceutical forms such as bath additives and liquids (used as inhalant) may be that they humidifies the respiratory gas and thus may contribute to increase the dissolution of the respiratory mucus.

Pharmacokinetic:

For Eucalyptus oil or its preparation no sufficient data are available. Therefore, no statements on pharmacokinetic of Eucalyptus oil preparations can be made.

Despite this fact the published data on 1,8-cineole should be taken into account. 1,8-cineole as the main constituent of the volatile oil of Eucalyptus is rapidly absorbed through skin and mucosa. Thus the oral use, the external use and the use by inhalation are plausible.

Although no interaction studies were published, a number of *in-vitro* and *in-vivo* animal studies indicate that 1,8-cineole affects the activity of liver enzymes. But tested concentrations are much higher than the concentrations which the traditional human dose can achieve; therefore, these findings are irrelevant for the monograph.

Toxicology:

Acute toxicity data on Eucalyptus oil are only available in rodents. Adequate tests on mutagenicity, carcinogenicity and reproductive toxicity are missing. Results for 1,8-cineole are not complete and furthermore can only be of limited value for the monograph on Eucalyptus oil. Therefore, a Community list entry cannot be recommended from a non-clinical point of view.

# 4. Clinical Data

## *4.1. Clinical Pharmacology*

### 4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Clinical data on pharmacodynamic properties of Eucalyptus oil are missing. But the effects of 1,8-cineole on human after inhalation have been evaluated. A study on twenty healthy humans showed that an inhalation of 100 µl 1,8-cineole led to an increased feeling of relaxation and a decreased reaction time [Ilmberger *et al*. 2001].

*Assessor's comment*
*The increased relaxation feeling, due to 1,8-cineole inhalation, may create a feeling of well-being in patients with coughs and colds. But this is not an objective analysis of symptoms of cold.*

### 4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Eucalyptus oil

Clinical data on Eucalyptus oil or its preparations are missing.

1,8-cineole

Inhalation
Pharmacokinetic of 1,8-cineole was investigated by Jäger *et al.* [1996] on 4 healthy subjects. 1,8-cineole was administered by a closed breathing circuit with the air passing over 4 ml of 1,8-cineole for 20 min. Blood samples were drawn at 0, 5, 10, 20, 25, 30, 35, 45 and 60 min after application. The results showed that 1,8-cineole is well absorbed from breathing air, with a peak plasma concentration after about 18 min. The elimination from blood is biphasic, with a mean distribution half-life of 2-13 min and an elimination half-life of 31-281 min.

The uptake of 1,8-cineole *via* inhalation was studied in one healthy subject by Stimpfl *et al*. [1995]. During an inhalation period of 20 min (2 ml 1,8-cineole 99%) the 1,8-cineole concentration in blood serum was increasing in an almost linear way from 4-20 min to a maximum. When inhalation was stopped, the concentration of 1,8-cineole in serum dropped immediately. After further 40 min, a reduced value of about 10% of the maximum value was observed. Stimpf *et al.* obtained a half-life of about 10 min. These results are in accordance with the results of Jäger *et al*. [1996].

Inhalation and oral use
Kohlert *et al.* [2000] reviewed the published data on bioavailability and pharmacokinetics of volatile terpenes. Concerning the above summarised study of Jäger *et al.* [1996], it was stated that there are substantial differences of elimination half lives in male and female subjects. Indeed elimination half lives were at least twice as long in female subjects, but it has to be considered that tested subjects were only 4 (2 male and 2 female). Concerning another study of Zimmermann *et al*. [1995], it was deduced that the upper part of the gastrointestinal tract has no significant role with respect to the absorption of 1,8-cineole. A study of Zimmermann was performed with capsules containing a mixture of limonene, 1,8-cineole and $\alpha$-pinene. 1,8-cineole was only measured as a marker. The results showed that an oral administration of 1,8-cineole led to a maximum of 1,8-cineole concentration in blood serum within 2.3-2.6 h for the unchewed tablet and within 0.7-1.1 h for the chewed tablet.

*Summary*

*Clinical data on pharmacology of Eucalyptus oil are missing. Studies on 1,8-cineole confirmed that it is well absorbed from breathing air. After an inhalation period of 20 min, plasma concentrations increased about 20 min. Distribution half-life obtained was between 2-13 min and elimination half-life was between 31-281 min. Oral administration led to a maximum blood serum concentration within 0.7-2.6 h.*

## *4.2. Clinical Efficacy*

Eucalyptus oil

Cutaneous use

Packman and London [1980] studied the antitussive effects of Eucalyptus oil in petrolatum based and "chest rub", a petrolatum base with menthol menthol, camphor, Eucalyptus oil, Turpentine oil, Cedar leaf oil, Myristica oil and thymol on citric acid aerosol induced cough in a single-blind cross-over study with 32 healthy subjects. The Eucalyptus oil formulation (7.5 g oil applied to chest and massaged 10-15 s) yielded statistically decreases in cough counts compared with baseline cough counts for up to 1.5 h. It also produced a significantly greater decrease than the oil of Turpentine oil or petroleum. Reduction of mean cough counts was from 10.8 at baseline to 8.8, 9.0 and 10.1 at 30, 60 and 90 min, respectively ($p<0.05$).

Hong and Shellock [1991] investigated the effects of a product containing Eucalyptus oil, lanolin and 15% menthol on cutaneous circulation and on skin and muscle temperature. Ten healthy subjects (aged 23-43) applied an amount of 2.5 cm length and 5 mm in diameter with total volume of 5 x 5 x 2.5 $cm^3$ on the upper forearm. There was no significant effect on the subjective effect, but an significant increase in cutaneous blood flow and skin temperature in comparison to placebo ($p<0.05$). The effects lasted 45 min.

Inhalation

Burrow *et al.* [1983] investigated the effects of camphor, Eucalyptus oil and menthol on the nasal resistance to airflow using rhinometric techniques and after 5 min exposure (face mask, 4 l/min by passing air from a cylinder containing 10 ml Eucalyptus oil) of 31 volunteers (aged 20-51, 26 male and 5 female). They were asked to describe the subjective effects on nasal sensation. Nasal resistance was technically measured while breathing through the test mask, before and after exercising for 5 min on a cycle ergometer. Objective measurements of nasal resistance showed no significant effect. Questionnaire yielded that the majority of subjects reported a cold sensation and an increase of nasal airflow after administration of Eucalyptus oil, camphor or menthol.

### 4.2.1. Dose response studies

No data on Eucalyptus oil or 1,8-cineole are available.

### 4.2.2. Clinical studies (case studies and clinical trials)

Eucalyptus oil

No studies on effect of Eucalyptus oil on patients with cold, coughs or muscle pain are available.

1,8-cineole

**Acute rhinosinusitis**

Kehrl *et al*. [2004] studied the efficacy and safety of 1,8-cineole capsules with placebo in 152 patients (aged 18-57) with acute rhinosinusitis. A dosage of 100 mg three times a day was administered for 7 days (75 patients placebo, 75 patients 1,8-cineole). Significant differences from the beginning to the

end of treatment for amelioration of headache on bending, sensitivity of pressure points of trigeminal nerve, nasal obstruction, secretion quantity and viscosity and rhinological secretion as well as for redness of mucosa was found. No significant differences were found according to clinical findings of inflammation such as conjunctivitis, tracheaitis, pharyngitis, and bronchitis. No differences have been found for parameters of leukocyte count and erythrocyte sedimentation rate. Authors concluded that the early treatment of sinusitis with 1,8-cineole can avoid antibiotic treatment. Mild side effects were observed in two patients as heartburn and exanthema.

In another study, 150 patients (aged 18-65) with acute and viral rhinosinusitis were treated with 1,8-cineole (3 x 200 mg) or a herbal combination product (Gentianae radix, Primula flos, Ramicis herba, Sambuci flos, Verbenae herba). Both treated groups showed an improvement in all relevant characteristics for rhinosinusitis within 7 days. A significant benefit after treatment with 1,8-cineole could be detected for bronchitis but not for pharyngitis, tracheitis and conjunctivitis. Scores for headache on bending, frontal headache, sensitivity of pressure points of trigeminal nerve, nasal obstruction and rhino-secretion for 7 day treatment were significantly lower for the treatment with 1,8-cineole than for herbal combination product [Tesche *et al.* 2008].

*Assessor's comment:*
*Sinusitis and its symptoms are difficult to score because of the individual perception. Ultrasonic or computed tomography studies have not been performed.*

**Pulmonary diseases**
Worth *et al*. [2009] studied the effects of 1,8-cineole (200 mg 3 times a day for 6 months as concomitant therapy) in comparison with placebo in a double-blind, placebo-controlled study (242 patients with chronic obstructive pulmonary disease; aged 40-80). 1,8-Cineole reduced exacerbations as well as dyspnea and improved lung function (forced expiratory volume (FEV), forced vital capacity (FVC), vital capacity (VC)) significantly in comparison to placebo. Worth *et al.* declared the therapy with 1,8-cineole only as a concomitant one. No information has been given on the other medications.

In order to compare the effects of oral therapy with 1,8-cineole (3 x 200 mg/day) and ambroxol (3 x 30 mg/day) after treatment over one week, a randomised double-blind, cross-over trial in 29 patients (average age 49) with chronic obstructive pulmonary disease (COPD) was performed by Wittmann *et al*. [1998]. All parameters of lung-function, peak-flow, and symptom-score showed better improvements under therapy with 1,8-cineole, but failed to reach statistical significance in comparison to ambroxol.

A double-blind placebo controlled study on 51 patients with COPD was carried out for 8 weeks by Habich and Repges [1994]. Both groups were treated with β2-sympathomimetics, glucocorticosteroids and methylxanthins and at the same time the testing group was treated with 200 mg 1,8-cineole 3 times a day. The objective lung function parameters airway resistance and specific airway resistance were reduced by 21% and 26%, which was both clinically relevant and statistically significant in comparison to the placebo group.

Dorow [1989] studied the effect of a 4-day therapy with 4 times oral administration of 200 mg 1,8-cineole on mucociliary clearance in patients with chronic pulmonary obstruction (n=12, aged 47-76). After 60 min and 120 min a significant improvement of mucociliary clearance was found in comparison to starting value.

Grimm [1987] conducted a non-placebo-controlled study on the efficacy of inhaled 1,8-cineole (3 times 20 drops a day inhaled for 3-5 min) on patients suffering from chronic bronchitis (n=10), acute bronchitis (n=3) or asthma (n=11). 23 out of 24 patients (aged 17-84) showed an increased expiratory peak flow. Undesirable side-effects have not been registered. Precise amount of applied 1,8-cineole is missing.

In 2001 Juergens *et al.* stated that a 1,8-cineole application in asthmatic patients led to an increased lung function. 600 µg 1,8-cineole per day decreased the necessary steroid therapy by about 36%.

Since 1,8-cineole had been found to have an inhibitory effect on inflammatory mediator production Juergens *et al.* [2003] performed a randomised, placebo-controlled trial to determine the oral glucocortoicosteroid-saving effect of long-term 1,8-cineole therapy in patients with severe asthma. All subjects received between 5 and 24 mg prednisolone, inhaled corticosteroids (expressed as equivalent doses to beclomethasone) and, additionally, long acting β-agonists and/or theophylline. Dosages were kept constant throughout the study except for short-acting β-agonists. Daily prednisolone dosage and concomitant asthma medication did not differ in the two groups. Each participant was randomly assigned either to 1,8-cineole (small gut soluble capsules, 200 mg t.i.d. for 12 weeks) or placebo capsules. Lung function test was performed and venous blood was taken to determine blood cells. 12 patients out of 16 remained clinically stable despite a reduction of oral steroid dosage of 5 mg every third week. The mean reduction of steroid dosage was 36% equivalent to 3.8 mg/day in the verum group which remained clinically stable, in contrast to the placebo group (7% equivalent to 0.9 mg/day, 12 out of 16 patients were not able to tolerate a decrease of oral steroids). Authors concluded that this is a confirmation of the anti-inflammatory activity of 1,8-cineole in bronchial asthma.

*Assessor's comment.*
*Findings of Juergens et al. [2003] are only relevant to patients suffering from asthma. Asthma is not a traditional use indication because its treatment should be supervised by a medical practitioner. Thus these findings are not relevant for establishing a monograph with traditional indications.*

*Summary:*

*Several studies dealt with effects of 1,8-cineole on pulmonary diseases, but none with Eucalyptus oil preparations. Therefore, these results are not sufficient to apply them to a well-established used or a traditional medication.*

*Bronchitis and asthma are not among potential traditional indications, but the above reported findings support the traditional use in symptoms of cough associated with cold, but not a well-established use indication.*

### 4.2.3. Clinical studies in special populations (e.g. elderly and children)

Clinical studies on children suffering from cold have not been published, but as described in section 1.2, preparations containing Eucalyptus oil are authorized for the German market also for children. Several preparations for oral and cutaneous use in children over 12 years of age and preparations for cutaneous use (bath additives, ointments, oil) are approved for administration in children over 2 years. Clinical studies or adequate reference to literature that was provided as part of the application documentation have been considered to be sufficient to confirm the safe use in children. See also HMPC opinion in section 5.5 concerning children under 4 years of age and concerning the contraindications.

Kenia *et al.* [2008] tried to confirm an effect of menthol on nasal airflow and cough counts after inhaled citric acid powder. To 42 children, aged 10-11 years, either menthol or placebo (both containing Eucalyptus oil 2 g or 0.5 g, respectively) was administered by 5-min inhalation. After inhalation of placebo (Eucalyptus oil) there was no significant difference in nasal airflow or cough count when compared to either baseline or menthol. These findings do not support a positive effect on cough of inhaled menthol or Eucalyptus oil, either.

*Summary:*

*Results on the efficacy of Eucalyptus oil are not consistently. A statistical decrease in cough counts was found on 32 healthy subjects after topical use of Eucalyptus oil in citric acid aerosol cough mode [Packman and London 1980]. On the other hand, inhaled Eucalyptus oil did not affect cough count or nasal airflow in a study conducted with 42 healthy children [Kenia et al. 2008]. Since in this study Eucalyptus oil was administered as placebo in doses of 0.5-2 g, it is possible that this is not an effective dose. A dose of 10 ml Eucalyptus oil showed no significant objective increase in nasal flow, but a subjective feeling of an increased air flow, that may be due to a sensation of cold.*

*Clinical studies on the efficacy of 1,8-cineole with 152 and 150 patients suffering from acute rhinosinusitis showed a significant improvement of headache on bending, sensitivity of pressure points of trigeminal nerve, nasal obstruction and rhinosecretion (quantity and viscosity). Oral doses ranged from 3 times 100 to 200 mg 1,8-cineole a day [Kehrl et al. 2004, Tesche et al. 2008].*

*Studies with patients suffering from chronic obstructive pulmonary disease COPD (number of patients: 242, 29, 51, 12) showed after oral administration of 3-4 times 200 mg 1,8-cineole an improved lung function, but did not always reach statistical significance. Additionally a study with 13 patients suffering from bronchitis and 11 patients suffering from asthma showed after inhalation of a 1,8-cineole containing liquid (20 drops, without information about amounts) an increase expiratory peak flow.*

*No sufficient data have been published for the oral use in children under 12 years of age. Therefore, the oral use should be limited to adolescents over 12 years of age. The cutaneous use has been approved in Germany for children over 2 years, but in accordance with other HMPC monographs on essential oils, the use is restricted to children over 4 years of age (see section 5.5 of this assessment report and sections 4.2 and 4.4 of the monograph).*

## *4.3. Overall conclusions on clinical pharmacology and efficacy*

Clinical data on pharmacology of Eucalyptus oil are missing, but studies on 1,8-cineole confirmed that it is well absorbed from breathing air and after oral administration. A topical application (bath additives, ointments, inhalant) may also lead to absorption of volatile components from breathing air. Additionally a good percutaneous absorption of 1,8-cineole from topical applied essential oils can be regarded as confirmed [Weyers and Brodbeck 1989].

Despite the long usage as nasal decongestants, there has been little research on the effects of Eucalyptus oil on nasal resistance to airflow. A reduction of cough counts after topical application of Eucalyptus oil has been confirmed, but a distinct improvement of nasal airflow after inhalation could not be shown for healthy subjects. Comparable studies on patient suffering from rhinosinusitis are missing.

Clinical studies with patients suffering from either acute rhinosinusitis, COPD or bronchitis or asthma have only be conducted with 1,8-cineole. All studies which applied 3-4 times 100-200 mg 1,8-cineole (oral) a day could confirm a positive effect on symptoms of cold and rhinosinusitis.

Eucalyptus oils contain not less than 70% of the major constituent 1,8-cineole, that probably contributes to the effects of Eucalyptus oil containing preparations. Traditional reported oral posology of 100-200 mg (200-1000 mg a day) Eucalyptus oil 2-5 times a day corresponds to 140-700 mg 1,8-cineole a day. A daily oral dose of 140-700 mg 1,8-cineole corresponds to 47% to 88% of dosages in published clinical studies for 1,8-cineole (330-800 mg a day). Therefore, an effect of Eucalyptus oil on symptoms of cough associated with cold is plausible.

Traditional topical posology ranges from 70-220 mg Eucalyptus oil (2-3 times a day: 140-660 mg a day) that corresponds to about 98-462 mg 1,8-cineole a day.

There are no sufficient clinical data on studies concerning the topical/inhalation use and the posology of liquids, bath-additives and semi-solid dosage forms. But it can be assumed that inhaled Eucalyptus oil stimulates cold receptors in the nose and that this gives a sensation of increased airflow. Findings that an inhalation of 1,8-cineole led to an increased relaxation feeling, may support a feeling of well-being in patients with coughs and colds that contributes to the benefits of Eucalyptus treatment. Thus, reported traditional posologies in the monograph are not supported by clinical data and based only on traditional data summarised in section 1.2 and 2.3.

There are no clinic data available that supports the use of Eucalyptus oil for the treatment of rheumatic complaints and/or muscular- and articular pain. Only the investigations of Hong and Shellock 1991 and Weyers and Brodbeck [1989] on combination products containing 1,8-cineole support the use for this indication because they found an effective amounts of 1,8-cineole at the target area in skeletal muscles and confirmed an increased cutaneous blood flow as well as an increased skin temperature after dermal application. Precise amounts of applied 1,8-cineole are not given, therefore the posologies given in the monograph are based only on traditional data.

# 5. Clinical Safety/Pharmacovigilance

## *5.1. Overview of toxicological/safety data from clinical trials in humans*

Local tolerance of Eucalyptus oil and Pine needle oil containing ointments (10 g or 5 g each/100 g) was studied by Willms *et al.* [2005]. 46 healthy volunteers showed no irritation of skin after application on the inside of lower arm. The amounts applied have not been reported.

## *5.2. Patient exposure*

Patch testing showed a positive reaction in a 53-year-old patient suffering from relapsing eczema after applying Eucalyptus oil 2% [Schaller and Korting 1995]. Also Darben *et al.* [1998] reported a case of Eucalyptus oil toxicity from topical application. A 6-year-old girl suffering from pruritic urticaria has been treated with 25–50 ml Eucalyptus oil per application for 1 h every 2-4 h for 2 days. After treatment the girl became unconscious. Six hours after presentation to the hospital the patient markedly improved.

A clinical study on 152 patients suffering from acute non-purulent rhinosinusitis showed mild side-effects such as heartburn and exanthema in two patients after oral intake of 100 mg 1,8-cineole 3 times a day [Kehrl *et al.* 2004].

## *5.3. Adverse events and serious adverse events and deaths*

Both the Commission E monograph and the standard license in Germany listed nausea, vomiting and diarrhoea as possible side effects. As contraindications, inflammatory diseases of the gastro-intestinal tract, gall bladder disease or impaired liver function have been given. Additionally, Eucalyptus preparations for cutaneous use should not be applied to the face, especially the nose, of infants or young children.

As discussed in section 3.2, the oil may induce liver enzymes that are involved in drug metabolism. Therefore, some monographs stated that the effects of other drugs may be influenced by concomitant medication [WHO monographs 2002, Blumenthal *et al*. 1998]. Having considered the amounts involved, these findings are irrelevant for the traditional posology (see section 3.2 of this assessment report).

A number of intoxication reports following accidental exposure to high doses of Eucalyptus oil are available in the literature. Already in 1910, Kirkness reported symptoms such as intense headache, vomiting, collapse, feeble pulse, subnormal temperature, girdle-like constriction around abdomen and dilated pupils after ingestion by mistake. Numerous case reports described the following effects of incidental ingestion and topical applications in adults and children: unconsciousness, vomiting, decreased deep tendon reflexes, hypotonia, gastrointestinal symptoms, central nervous system (CNS) depression, rapid shallow respiration, rapid and feeble pulse, hypothermia, headache, dizziness, burning sensation in the mouth nose and gastric burning, nausea, vomiting, dizziness and muscular weakness, miosis, tachycardia and feeling of suffocation [Patel and Wiggins 1980, Hindle 1994, Darben *et al.* 1998, Anpalhan and Le Couteur 1998, Spoerke *et al.* 1989, Webb and Pitt 1993]. A summary of case reports by De Vincenzi *et al*. [2002] listed ingested amounts ranged from 1 ml to 220 ml that caused these side-effects. Surprisingly after dialysis two patients survived despite 21-220 ml ingestion, while 2 patients died after an ingestion of only 3.5-5 ml. Darben *et al.* [1998] reported occurrence of death from CNS depression after ingestion of 30 ml oil and Saller *et al*. [1988] cited a lethal dose for adults of only 4-5 ml Eucalyptus oil.

A case report by Shishir *et al.* [2011] described the occurrence of oral mucosa injury caused by topical application of Eucalyptus oil over gums.

Tibballs [1995] conducted a retrospective analysis of case histories of 109 children (aged 0.5-107 months, mean age 23.5 months) admitted to hospital with a diagnosis of Eucalyptus oil poisoning (unknown doses because of accidental ingestion). Additional investigations of 27 patients (aged 0.5-72 months; medically poisoned) showed nil effects such as spluttering or coughing after a mean ingestion of 1.7 ml oil, minor poisoning such as ataxia, vomiting, abdominal pain or miosis after 2 ml, moderate poisoning such as depression of conscious state or Glascow coma scale score of 8-14 after 2.5 ml and major poisoning such as unconsciousness and Glascow coma scale score of 3-7 after ingestion of 7.5 ml. The lowest amount of 1.7 ml (~1,700 mg) within these case reports is more than the 8-fold amount of the single dose recommended for adults and adolescents. Therefore these effects have to be judged as effects after overdose.

In general, an anti-poisoning treatment with activated charcoal and dialysis is recommended.

1,8-cineole

Melis *et al.* [1990] reported the following symptoms of poisoning with 1,8-cineole described by parents: nose and gastric burning, nausea, vomiting, dizziness and muscular weakness, miosis, tachycardia and feeling of suffocation in infants aged 1 month to 3 years and 9 months.

These findings are in accordance with the reported symptoms of poisoning with Eucalyptus oil.

*Summary*

*Because of its strong odour, an accidental poisoning by Eucalyptus oil seems to be not very likely, but nevertheless numerous case reports have been published. Safe dosage as an internal medication is difficult to define, because of the variations in response to similar amounts, which may result from individual idiosyncrasy and inconsistent compositions of ingested preparations [Gurr and Scroggie 1965]. Data on death caused by consumption of Eucalyptus oil in humans are not consistent. Death has occurred after ingestion of only a few ml of the oil while other people recovered even after consuming amounts in the range of 21-220 ml.*

*Allergic reaction may occur after topical application in sensitive patients. Extensive topical application can lead to the same symptoms as an oral overdose.*

*Since the standard license in Germany (basis of traditional use in Germany) listed some contraindications, contraindications and special warnings have been worded in accordance to other monographs (such as Menthae piperitae aetheroleum). See in section 5.6 of this assessment report.*

*Findings of Tibballs [1995] concerning children under 6 years of age, are not relevant for the monograph, because oral application is not recommended for children under 12 years of age.*

## *5.4. Laboratory findings*

No data are available.

## *5.5. Safety in special populations and situations*

Young children

It has been described that the inhalation of essential oils, particularly observed for menthol and camphor, may lead to an irritation of the nasal mucosa which could lead to a closure of glottis in infants (Kratschmer-Reflex) [Jorch 2009]. Due to the cooling effect and strong odour of Eucalyptus oil preparations, it is recommended that ointments should not be applied to or near the face of babies and very young children because of the risk of reflex spasm of the glottis [ESCOP 2003, Blumenthal *et al.* 1998]. Even apnoea may occur [Blaschek 2007].

Since essential oils are steam volatile components, the use as an oral fluid (including capsules with oil) or an inhalant could also generate the risk of reflex spasm for babies and very young children. Therefore, the use in children with a history of seizures should be contraindicated.

The HMPC considered the use in children under 4 years of age as generally not recommended in traditional use, due to considerations concerning clinical safety for this age group where medical advice should be sought. After discussion on Eucalyptus folium (meeting January 2013), the HMPC decided that the use must be contraindicated in children below 30 months.

Pregnancy and lactation

There is no information available on precaution concerning Eucalyptus applications in pregnant or nursing woman. Since human data are not available and 1,8-cineole has been reported to penetrate the placenta in rodents, Eucalyptus oil should not be taken during pregnancy or lactation [WHO 2002, ESCOP 2003].

Concomitant medication

On order to investigate whether 1,8-cineole treatment affects plasma levels of other drugs, Jori *et al.* [1970] studied the plasma levels of 5 volunteers after administration of aminopyrine. During treatment with 1,8-cineole (inhalation for 10 min of a 0.4 g 1,8-cineole suspension) and aminopyrine (600 mg orally before and after treatment with 1,8-cineole) for 10 days, it has been observed that 1,8-cineole treatment increased the disappearance of plasma aminopyrine in 4 out of 5 subjects.

## *5.6. Overall conclusions on clinical safety*

For extensive oral and topical application numerous side-effects on gastrointestinal tract, respiratory system, central nervous system, consciousness etc. have been reported:

Because there is a risk that 1,8-cineole containing preparations, like other essential oils, can induce laryngospasm, children under 2.5 years of age should be excluded from cutaneous use and inhalation.

The Commission E monograph “Eucalyptus oil” gives some side-effects and contraindications as follows:

oral use:
contraindications: “Inflammatory diseases of gastrointestinal tract and bile duct, significant liver diseases.”
side-effects: “In rare cases nausea, vomiting and diarrhoea may occur.”

cutaneous use:
contraindications: “Eucalyptus preparations for cutaneous use should not be applied to the face, especially the nose, of infants or young children.”

Reporting system in Germany listed the following side effects for Eucalyptus oil containing medicinal products for adults (no differences between soft and gastro-resistant capsules have been detected):

oral use:
allergic skin reaction (1), shock (1), tremor (1), decreased blood pressure and increased pulse (1), cold sweat (1), dizziness (3), tiredness (1), coordination abnormal (1), ataxia (1), aphasia (1), syncope (1), vomiting (1), urticaria (1)

topical use:
skin disorders such as pustular rash (2); skin irritation (1), contact allergy (2), bullous eruption (2, vomiting (after overdose, 1).

From clinical trials, mild side-effects after ingestion of 1,8-cineole such as heartburn and exanthema have been observed only in a small number of treated patients. In literature, reported side-effects have only been described in case reports of accidental overdose but not in a dose near the traditional posology.

Allergic skin reactions due to Eucalyptus oil exposure have been reported in patients suffering from dermatosis. However Opdyke [1975] concluded that Eucalyptus oil is generally non-irritating, non-sensitizing in animal and in patch tests with healthy human volunteers. Only a few mild side-effects that have been occurred in the Reporting system in Germany, therefore they are not included in the monograph.

Based on data on clinical safety and based on the given contraindications for already authorised preparations containing Eucalyptus oils as well as already established HMPC monographs on other essential oils and Eucalyptus folium, several contraindications and special warnings should be given in sections 4.3 and 4.4 of the monograph as follows:

**Section 4.3 Contraindications**

“Hypersensitivity to the active substance or 1,8-cineole.
Children with history of seizures (febrile or not).

Children under 30 months of age, because there is a risk that 1,8-cineole containing preparations, like other essential oil can induce laryngospasm.

Full hot baths are contraindicated in cases of large skin injuries and open wounds, acute skin diseases, high fever, severe infections, severe circulatory disturbances and cardiac failure.”

**Section 4.4 Special warnings and precautions for use**

“The use is not recommended in children between 2.5 and 4 years of age, as there is no sufficient experience available.

Cutaneous use:
Eye contact with unwashed hands after the application of eucalyptus oil, may potentially cause

irritation.
Eucalyptus oil should not be applied on broken or irritated skin.

Oral use:
Eucalyptus oil should be used with caution in inflamed and ulcerated conditions of the gastrointestinal tract.
Indication 1)
When dyspnoea, fever or purulent sputum occurs, a doctor or a qualified health care practitioner should be consulted.
The oral use and in children under 12 years of age has not been established due to lack of adequate data.
Indication 2)
When reddening or swelling of the aching parts occur a doctor or a qualified health care practitioner should be consulted."

The proposed wording is in accordance with other monographs.

Due to its circulation enhancing effect, an irritating effect on gastrointestinal tract is plausible. Whereas a choleretic effect of Eucalyptus oil or 1,8-cineole has not been described. Therefore, a special warning in section 4.4 concerning liver diseases is not given.

The results of Jori *et al*. [1970] on inhaled 1,8-cineole indicate that the effect of other drugs may be influenced by concomitant administration. But the posology of 1,8-cineole tested by Jori *et al*. corresponds to about 571 mg Eucalyptus oil. This does not correspond to the traditional single dose recommended for inhalation. Animal studies on the inhibitory effects of effect of 1,8-cineole on liver and lung microsomal cytochrome P-450 and b5 after s.c. injection or by aerosol inhalation confirmed these findings. Therefore, the Commission E had warned about possible interactions with other drugs: "The oil may induce liver enzymes that are involved in drug metabolism." However, reported interactions have been found for higher concentrations than the proposed traditional posology. Thus, these interactions are not given in the monograph.

# 6. Overall conclusions

Clinical data on efficacy of Eucalyptus oil preparation are not available, thus a well-established use is not supported. Non-clinical and clinical data on 1,8-cineole support that an effect of Eucalyptus oil on upper respiratory diseases and in muscular pain is plausible.

Due to that and its widespread and long-standing use, Eucalyptus oil can be accepted for traditional use for the relief of symptoms of coughs and colds and for the external use in localised muscle pain. Administration forms are liquids (topical, oral or as inhalant), capsules (soft and gastroresistant), bath additives (cutaneous use) and semi-solid dosage forms (cutaneous use). Since traditional herbal medicinal products are only oral, external or/ and inhalation preparations according to Article 16a of Directive 2001/83 EC, products intended for intramuscular or subcutaneous injection cannot be described in the monograph.

Since inhaled Eucalyptus oil stimulates cold receptors in the nose it causes a sensation of increased airflow. Additional findings that an inhalation of 1,8-cineole led to an increased relaxation feeling, may also support a feeling of well-being in patients with cough and contribute to the benefits of Eucalyptus treatment. However, a stimulation of cold receptors can lead to a closure of glottis in children under 30 months of age.

Due to their volatile substances bath additives and semi-solid dosage forms may act as inhalant as well as percutaneously. Therefore, their benefits for the treatment of muscle pain as well for symptoms of cough are plausible.

Reported indications for rheumatic complaints, asthma and bronchitis have not been taken in the monograph, because they should be supervised by a medical practitioner.

Relevant data on oral use in children under 12 years and cutaneous use in children under 4 years are not available and therefore, in the monograph, the use in these populations is not recommended.

Sufficient data on toxicity of Eucalyptus oil are not available. Non-clinical data on toxicity of Eucalyptus oil pointed to an increased occurrence of mitotic recombinants. But tests on human leukemic K 562 cells showed neither DNA-damaging nor DNA-protective effects of 1,8-cineole and no relevant data on the carcinogenicity of Eucalyptus oil or 1,8-cineole to humans are available.

Safety during pregnancy and lactation has not been established, only animal studies indicate that 1,8-cineole can cross the placenta barrier, but not the blood milk barrier. Due to the lack of adequate data, the following wording should be given in section 4.6 of the monograph: “Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.”

Due to the lack of sufficient toxicity data, a Community list entry cannot be supported.

# Annex

## *List of references*