EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 March 2024
EMA/HMPC/320282/2023
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Eucalytus globulus* Labill.; *Eucalyptus polybractea* R.T. Baker; *Eucalyptus smithii* R.T. Baker, aetheroleum

Draft – Revision 1

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Eucalyptus globulus* Labill.; *Eucalyptus polybractea* R.T. Baker; *Eucalyptus smithii* R.T. Baker, aetheroleum
Herbal preparation(s)	Essential oil
Pharmaceutical form(s)	Herbal preparations in solid dosage forms for oral use. Herbal preparations in liquid dosage forms for inhalation, cutaneous use and bath additives. Herbal preparations in semi-solid dosage forms for cutaneous use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.

First assessment	Rapporteur	J. Wiesner
	Peer-reviewer	R. Hönow
Revision	Rapporteur	J. Wiesner
	Peer-reviewer	I. Chinou

Note: This draft assessment report is published to support the public consultation of the draft revised European Union herbal monograph on *Eucalytus globulus Labill.*; *Eucalyptus polybractea*

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

R.T. Baker; *Eucalyptus smithii* R.T. Baker, aetheroleum. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on 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 revised monograph.

Table of contents

1. Introduction

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

- Herbal substance(s)

Eucalyptus leaf (Eucalyptus folium) is defined as 'whole or cut, dried leaves of older branches of *Eucalyptus globulus* Labill.' The essential oil content of the leaves is defined with minimum 20 mL/kg (anhydrous drug) for the whole drug and minimum 15 mL/kg (anhydrous drug) for the cut drug (European Pharmacopoeia: 07/2014:1320).

The genus Eucalyptus belongs to the family of Myrtaceae, subfamily Myrtoideae. The eucalyptus tree is native to the subtropical rain forest of South Australia and Tasmania. Over 600 Eucalyptus species form the bulk of the trees in Australia.
The commercially available drug for the production of the oil is cultivated in many parts of the world. The main producer regions of *Eucalyptus globulus* are the Mediterranean, North Africa, the Caucasus, Florida, California, Brazil, Mexico, Jamaica and India. *Eucalyptus smithii* is cultivated in Brazil, Guatemala, Hawaii and at the French Atlantic coast as well as the Caucasus and *Eucalyptus polybractea* occurs only in Australia, especially in Victoria and New South Wales (Blaschek et al., 2021).

For the leaves of *E. globulus* a content of essential oil of 1.8-2.5% has been reported, for the leaves of *Eucalyptus polybractea* 1.2-2.5% and for the leaves of *Eucalyptus smithii* 1.2-2.2% (Blaschek *et al*., 2021).

- Herbal preparation(s)

The essential oil is defined in the European Pharmacopoeia (07/2021:0390): 'Essential oil obtained by steam distillation and rectification from the fresh leaves or the fresh terminal branchlets of various species of Eucalyptus rich in 1,8-cineole. The species mainly used are *Eucalyptus globulus* Labill., *Eucalyptus polybractea* R.T.Baker and *Eucalyptus smithii* R.T.Baker.'

Major constituents of the essential oil

The main constituent of the volatile oil derived from fresh leaves of Eucalyptus species is 1,8-cineole. Beside 1,8-cineole, the oil contains monoterpenes such as myrtenol, α-pinene, β-pinene and pinocarvone (Blaschek et al., 2021). Silvestre et al. (1997) reported, 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.

The monograph of the European Pharmacopoeia opens the pharmaceutical use for various species of Eucalyptus, rich in 1,8 cineole. It specifies the following contents of components of the essential oil:

- 1,8-cineole: minimum 70.0%
- α-pinene: 0.05 to 10.0%
- β-pinene: 0.05 to 1.5%
- sabinene: maximum 0.3%
- α-phellandrene: 0.05 to 1.5%
- limonene: 0.05-15.0%
- camphor: maximum 0.1%.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of

vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

There are combinations on the European Market, which are combining essential oils of different plants adding additional information for the safety of the traditional use. This monograph refers exclusively to mono-preparations.

1.2. Search and assessment methodology

For the first HMPC monograph data bases PubMed (April 2011) and DIMDI – DB (Deutsche Institut für medizinische Dokumentation und Information, XMEDALL, 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.

Revision 1
For the revision 1 of the monograph a search was performed for the period of January 2013-February 2023 in EBSCO Discovery database (Medline Complete, Pub Med, Embase, DynaMed). Key words were Eucalyptus" and "Eucalyptus oil", language English. Further searches were performed with additonal key words as "clinical study", "toxicology" and "adverse events". Additional hand searches were performed in books, book chapters, articles and letters in Journals, Medical press reviews, acts of law and regulations in the BfArM owned library. The bibliographies of included trials and other relevant reviews were searched to identify further potential trials. Pharmacovigilance resources were the EudraVigilance database (EVDAS) and information provided by the Member States. A search was performed for the period of 01.01.2013-1.03.2023 in EVDAS (EudraVigilance) data base and national database. Key words were »Spontaneous, Other, Not available to sender (unknown), Report from Studies, suspect interacting, from the European economic area (EEA).

The EURD-list was checked if a PSUSA-procedure has been finalised during the review period.

A check of consistency (e.g. scientific decisions taken by HMPC) with other monographs was performed.

1.3. Main changes introduced in the first revision

During the first revision new information on medicinal use from products on the market and herbal preparations, indications and posologies fulfilling traditional use have been introduced in chapter 2. 'Data on medicinal use'.

Regarding chapter 3. 'Non-Clinical Data', additional non-clinical pharmacology studies have been published since the first version of the monograph. However, no substantial new findings were identified during the first revision and only a few new references were added. In addition, some references were considered not relevant during the first revision and were deleted.

In chapters 4. 'Clinical Data' and 5. 'Clinical Safety/Pharmacovigilance' additional studies have been introduced. Some references were considered not relevant during the first revision and were deleted. According to assessment of published literature and Eudravigilance data, undesirable effects were added.

To be consistent with other essential oil monographs the age limit for contraindication in younger children was adapted.

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form, posology	Regulatory Status
Eucalypti aetheroleum	For the short-term relief of respiratory tract disorders in children from 30 months of age.	Suppository, 46.1 mg, rectal use SD=1 suppository DD= 2 suppositories (in the morning and in the evening) The proposed dose (of 2 suppositories per 24 hours) cannot be exceeded. Contraindication: children under 30 month Duration of use: not over 3 days	2018, BE, THMP Withdrawn date: 20/01/2023
Eucalypti aetheroleum	Cough and cold with persisting mucus.	Oral use *Adults and adolescents over 12 years of age:* SD=100-200 mg DD=300-600 mg	WEU, 1976, DE
Eucalypti aetheroleum	a) Treatment of diseases of the upper respiratory tract. b) Treatment of rheumatic complaints.	Internal use: SD=2-4 drops on sugar or in a glass of warm water for drinking DD=6-12 drops Inhalation: SD=3-4 drops in hot water DD=9-12 drops External use: rub a few drops on the chest and back External use: rub a few drops on the affected area or aching part	Standard-zulassung, 1996, DE
Eucalypti aetheroleum	Treatment of diseases of the upper respiratory tract.	liniment (10% m/m) *Adults, adolescents and children over 2 years of age:* Rub a 2-3 cm string of ointment 4 times a day on chest and back	WEU, 1976, DE
Eucalypti aetheroleum	Treatment of rheumatic complains.	liniment (10% m/m) *Adults and adolescents:* 2-4 times daily as a thin layer on the affected area	WEU, 1976, DE
Eucalypti aetheroleum	a) Colds, symptoms of upper respiratory tract with persisting mucus.	liniment (10%) *Adults and adolesence:* 6 cm ointment 2-3 times daily *Children of 4-12 years:* 3 cm ointment 2-3 times daily, on the affected area (chest and back	WEU, 1990, DE

Active substance	Indication	Pharmaceutical form, posology	Regulatory Status
	b) Treatment of rheumatic complains.	or aching parts) *Adults and adolescents:* 6 cm ointment 2-3 times daily	
Eucalypti aetheroleum	Treatment of diseases of the upper respiratory tract	as bath additive *Adults, adolescents and children over 2 years of age:* 1.5-6 g Eucalyptus aetheroleum/ 100 l water 10-20 minutes, 3-4 times per week	WEU, 1976, DE
Eucalypti aetheroleum	Treatment of diseases of the upper respiratory tract.	bath additive *For children over 2 years*: 2.1 g Eucalyptus aetheroleum/ 100 l water 3-4 times per week	WEU, 1976, DE
Eucalypti aetheroleum	Treatment of diseases of the upper respiratory tract; treatment of rheumatic complains	bath additive *Adults, adolescents and children over 2 years of age:* 2.7- 3.6 g Eucalyptus aetheroleum/ 100 l water; at 35-38°C 10-20 min, 3-4 times per week	WEU, 1976, DE
Eucalypti Aetheroleum	Traditional herbal medicinal product used for relief of cough associated with cold.	bath additive *Adults and adolescents over 12 years of age:* 2-6 g Eucalyptus aetheroleum/ 100 l water 3 to 4 times a week *Children over 4 to 11 years of age:* 2-3 g Eucalyptus aetheroleum/ 100 l water 3 to 4 times a week	THMP, 2020, DE

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

In many countries, Eucalyptus oil is used in combinations with other essential oils. The combinations are usually administered in the field of indications of the mono-preparations, for the treatment of complaints associated with colds or for the treatment of rheumatic complains symptomatic relief of localised muscle pain.

Combination products are not assed in this review. This monograph refers exclusively to mono-preparations containing Eucalyptus oil.

Information on other products marketed in the EU/EEA (where relevant)

The major constituents of the essential oil is 70% 1,8-cineole. On the market are products of the substance 1,8-cineole. In this assessment report are included preclinical and clinical supportive data of this major constituent.

1,8-Cineol (Eucalyptol) was evaluated as component of natural sources of flavourings by the Committee of Experts on Flavouring Substances of the Council of Europe (CEFS), resulting in the allocation of a provisional TDI of 0.2 mg/kg bw. This TDI was derived from a minimum lethal dose of 60 mg/kg bw for children applying a safety factor of 300 (SCF, 2002).

2.1.2. Information on products on the market outside the EU/EEA

Eucalyptus oil is added in the List "Substances added to food" by the FDA (FDA, 2022). 1-8-Cineol (Eucalyptol) has been approved by the US Food and Drug Administration (FDA) for food use. The FDA advisory review panels on over-the-counter drugs have concluded that eucalyptol is safe for a variety of products, such as lozenges taken every 30-60 min at 0.2–15 mg or taken every 2 hrs at 1–30 mg of eucalyptol (SCF, 2002; quoting FDA, 1976 – 1990).

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). Eucalyptus preparations, including Eucalyptus oil, have been used by about 12% of asthmatic patients in USA and Mexico border population (Rivera et al*.,* 2004).

2.2. Information on documented medicinal use and historical data from literature

Herbal preparations derived from Eucalyptus spec. are used worldwide and Eucalyptus belong to the most popular medicinal plants of the world and have a long tradition in Europe. Although the original inhabitants of Australia, the aboriginal people, already took advantage of the medicinal benefits of Eucalyptus oil (Sherry et al., 2001), little or no reference to eucalyptus oil can be found in the books upon material medica published before the second half of the 19th century (Boyd & Pearson, 1946). One of the first eucalyptus oil monographs in Europa was that of Köhler (1873) with summarizes all available published information on the plant, preparations, efficacy and safety of the essential oil.

Madaus (1938) summarized old historical references and traditional uses from different countries of the world as Australia, India and Brasilia. He reported traditional uses in context of cough and cold, asthma, influenza, diabetes, rheumatic diseases etc. Also anecdotal potential antidiabetic effects have been described (Faulds, 1902) for eucalyptus oil.

There is a consistency in actual phytotherapeutic literature for the use in catarrhs of the respiratory tract (oral treatment, inhalation, topical use) and for the topical use in context of rheumatic complaints / localized muscle pain:

Monographs and related to efficacy and safety are e.g.: German Commission E monograph (1986), German Commission B monograph (bath-monograph) (1989), ESCOP monograph (2003); WHO monograph (2002), referencing often older publications.

Lemos *et al*. (2016) performed an ethnobiological survey of plants and animals used for the treatment of acute respiratory infections in children of a traditional community in the municipality of Barbalha, Ceará, Brazil. According to the relative frequency of citation (RFC) one of the most cited was *Eucalyptus globulus* (0.59). The ways of traditional use is tea (infusion and decoction) of the leaf, and inhalation in flu, nasal congestion, sinusitis, fever, cough.

Table 2: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Strength (where relevant) Posology Duration of use**	**Reference**
Eucalypti aetheroleum	internal and topical use: catarrhs of the respiratory tract	Internal use: Daily dose: 0.3-0.6 g	Commission E, 1986 Blumenthal et

Herbal preparation	Documented use / Traditional use	Strength (where relevant) Posology Duration of use	Reference
	External use: rheumatic complaints	External use: 5-20% in oil liniments and soft liniments 5-10% in water-ethanolic liquids pure essential oil: rub a few drops on the skin	al., 2000 [quoting Commission E, 1986; Wichtl and Bisset, 1994; Newall et al., 1996, Reynolds et al., 1989]
Eucalypti aetheroleum	Internal use: Adjuvant treatment of chronic obstructive respiratory complaints including bronchitis and bronchitis and bronchial asthma. Symptomatic relief of colds and catarrh of the upper respiratory tract. External use: Symptomatic treatment of colds and rheumatic complaints.	Internal use: Single dose: 0.05-0.2 ml Daily dose: 0.3-0.6 ml In capsules: 100-200 mg 2-5 times daily As a lozenge: single dose 0.2-1.5 mg every 0.5-1 hour. Inhalation: 12 drops per 150 ml or 1.5% solution (15 ml per 1 l water), up to 3 times daily. As liniment: Liniment containing 25% V/V of essential oil As ointment: Ointment containing 1.3% V/m, up to 3 times daily	ESCOP, 2003 [quoting: Hagers' Handbuch der Pharmazeutischen Praxis, 1993; Kasper et al., 1994; Wittman et al., 1998; Mahlo, 1990; Juergens et al., 2003; Reynolds & Prasad, 1982; Van Hellemont, 1988; Schilcher, 1997]
Eucalypti aetheroleum	Internal use and external use: catarrh of the respiratory tract External use: rheumatic complaints	Internal use: Daily dose: 0.3-0.6 g Single dose: 3 to 6 drops several times a day in warm water for drinking; 2-3 drops in hot water (80°C) for inhalation Single dose: 0.2 g or 10 drops External use: 5-20% in oil liniments or soft liniments, 5-10% in water-ethanolic liquids 20% in liniments	Blaschek et al., 2007; Blaschek et al., 2021 [quoting: Commission E, 1990 Standard-zulassung, 1987 Schultz&Schmid, 1984]
Eucalypti aetheroleum	Internal use as symptomatic treatment of catarrh and coughs. Topically as a rubefacient for treatment of	Internal use: Oral use: DD: 0.3-0.6 ml; 200-1000 mg (divided into several times daily) Inhalation: 12 drops/150 ml boiling water External use: DD: several drops or 30 ml	WHO, 2002 [quoting Comission E, 1990; Reynolds et al., 1996; Leung&Foster, 1996; Van Hellemont, 1988;Newell et al., 1996]

Herbal preparation	Documented use / Traditional use	Strength (where relevant) Posology Duration of use	Reference
	rheumatic complaints.	essential oil in 500 ml lukewarm water rubbed into skin; 5-20% in liquid or semisolid preparations; 5-10% in hydroalcoholic preparations	
Eucalypti aetheroleum	Mucolytic and antiseptic effects	Internal use: Inhalation: 15 drops in 150 ml hot water Oral use: 0.10-0.20 g (capsules) 2-5 times daily (=daily dose=0.2-1 g) for adults. Syrup: 0.025 in 100 ml: 2-4 table spoons a day. External use as antiseptic: Alcoholic liquids 3%; Pomade 2%	Pharmacopée Française, 1978
Eucalyptus aetheroleum	Adjuvant treatment of acute and chronic catarrh of the upper respiratory tract. Adjuvant treatment of rheumatic complaints.	Children between 4 and 12 years of age, adolescents, adults and elderly Eucalyptus oil: minimum 0.01 g of 1.8-Cineol per litre water (=app. minimum 1.4 g essential oil per 100 litter bath water) 3-4 times per week	Commission B, 1989

2.3. Overall conclusions on medicinal use

From the overview of data on marketed products in the EU it can be seen that Eucalyptus essential oil is marketed as "well-established products" and as well as "traditional used preparations". One preparation was registered in the pharmaceutical form of suppositories, what does not fulfil the criteria of long medicinal, traditional use.

Based on products existing in the market for more than 30 years, corresponding monographs and diverse contributions in the scientific literature, traditional use is demonstrated for Eucalyptus aetheroleum. The data described in section 2.1 and 2.2 reveal two different areas of indications which were acceptable for a traditional use monograph. The licenced/described indications are:

- for oral use, inhalation and cutaneous use: relief of cough associated with cold, adjuvant in acute and chronic catarrhs of the respiratory tract, adjuvant in upper airways inflammations with difficult expectoration
- for cutaneous use: treatment of rheumatic complaints, symptomatic relief of localised muscle pain.

The wording in the respective monograph was adjusted to the wording used for similar indications:
Indication 1) Traditional herbal medicinal product used for relief of cough associated with cold.
Indication 2) Traditional herbal medicinal product used for the symptomatic relief of localised muscle pain.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
Eucalyptus aetheroleum in solid dosage form for oral use	Indication 1): Traditional herbal medicinal product used for relief of cough associated with cold.	Oral use *Adolescents, adults and elderly* SD=100-200 mg, 2-5 times daily DD=200-600 mg	at least since 1976
Eucalyptus aetheroleum in liquid dosage form for inhalation and cutaneous use	Indication 1): Traditional herbal medicinal product used for relief of cough associated with cold. Indication 2): Traditional herbal medicinal product for the symptomatic relief of localised muscle pain.	<u>Inhalation:</u> *Adolescents, adults, elderly* SD=3-8 drops per 250 ml boiling water, 3 times daily *Children between 3 and 12 years of age* SD=2-4 drops per 250 ml boiling water, 3 times daily <u>Cutaneous use:</u> *Adolescents, adults and elderly and children between 3 and 12 years of age* Rub a few drops on the skin on chest and back, 2-3 times daily <u>Cutaneous use:</u> *Adolescents, adults and elderly and children between 3 and 12 years of age* Rub a few drops on the skin of the affected area, 2-3 times daily	since 1978
Eucalyptus aetheroleum in semi-solid dosage forms for cutaneous use (liniments 10%)	Indication 1): Traditional herbal medicinal product used for relief of cough associated with cold. Indication 2): Traditional herbal medicinal product for the symptomatic relief of localised muscle pain.	<u>Cutaneous use</u> *Adolescents, adults, elderly and children from 3 years of age* Apply a thin layer on chest and back 2-3 times daily <u>Cutaneous use</u> *Adolescents and adults* Apply a thin layer on the skin of the affected area 2 to 3 times daily	since 1976
Eucalyptus aetheroleum in liquid dosage form as bath additive	Indication 1): Traditional herbal medicinal product used for relief of cough associated with cold.	<u>Use as bath additive</u> *Adolescents, adults and elderly* SD=1.5-6 g essential oil/100 l water, 3 to 4 times a week *Children between 3 and 11 years of age* SD=0.5-3 g essential oil/100 l water, 3 to 4 times a week Recommended bath temperature is 35-38°C, 10-20 minutes.	since 1976

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	Indication 2): Traditional herbal medicinal product for the symptomatic relief of localised muscle pain.	Use as bath additive *Adolescents, adults and elderly* SD=2.7-3.6 g essential oil/100 l water, 3 to 4 times a week *Children between 3 and 12 years of age* Single dose: 0.5-3 g essential oil/100 l water, 3 to 4 times a week Recommended bath temperature is 35-38°C, 10-20 minutes.	

From the marked overview, ointments/ liniments with 10% are reported. In literature, usually dose ranges and no fixed doses are recommended. For example, the Commission E monograph recommends 5-20% Eucalyptus aetheroleum in oil liniments or soft liniments. The concentration of 10% from the traditional used preparations on the market is supported from literature.
The ointments are traditionally usually used "as a thin layer on the skin of the back and/or the chest". So, the traditionally used doses are strong depending on the size (and age) from the individual patient.
Hypothetically, the dose can estimated as follow: if an ointments is typically packed in tubes with an common opening of about 0.5 cm; 2-3 cm ointment are approximately 0.4-0.6 ml and 6 cm are 1.2 ml; with an average density 0.92 g/ml for the ointment it means that a single doses for such an ointment/tube ranges from 0.04–0.11 g eucalyptus oil.

Bath additives are on the market as products with app. 14-30% eucalyptus oil. The marketed products show a long traditional use for a dose range from 1.5-6 g eucalyptus oil per 100 l bath water, for all licenced age groups (children from 2 years, adolescents, adults). The monograph "Eukalyptusöl- Bäder" of the German Commission B (1989) recommends a posology for the eucalyptus aoil essential oil corresponding to a minimum of 0.01 g of 1.8-Cineol /=0.014 g eucalyptus oil per one litter bath-water /= minimum 1.4 g eucalyptus oil per 100 l bath water. The dose is given for all age groups, only infants and toddlers are excluded. The traditional used doses of eucalyptus oil baths are in a wide range (1.5-6 g per 100 l bath water). Some existing marketed products, intended for the use in children, recommend doses corresponding with the lower half of the traditional used range. This is in accordance with the general traditional uses, where for children are use the lower doses of a dose ranges. So, for the use in children only a low dose of 1.5-3 g per 100 l water is recommended for the HMPC monograph.

3. Non-Clinical Data

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

Several reviews exist in which the pharmacodynamic effects of eucalyptus oil are discussed. Some should be mentioned exemplary.

Barbosa *et al*. (2016) reviewed 68 out of 900 species and subspecies of the Eucalyptus genus on the antimicrobial, acaricidal, insecticidal and herbicidal properties. Dhakad et al. (2018)

summarized the results from test on e.g. antimicrobial, antihyperglycemic, antihelminthic, antiviral, antihistaminic, anti-inflammatory, antimalarial activities. In the review of Sandner et al. (2020) the immunomodulatory activities were described. Mieres-Castro et al. (2021) discus the main findings of eucalyptus oil as an antiviral agent and the mechanism thereof. Elangovan & Mudgil (2023) summarized the literature on the antibacterial properties of Eucalyptus globulus essential oil against methicillin-resistant Staphylococcus aureus (MRSA). Ridouh & Hackshaw (2022) summarized studies in animal models of neuropathic pain.

3.1.1. Primary pharmacodynamics

Antimicrobial activity

In vitro

Eucalyptus oil

Harkenthal *et al.* (1999) analysed eucalyptus oil (Ph.Eur.) by GC-MS and tested it against various bacteria using a broth microdilution method (against other essential oi, no positive control included). MICs against 8 Gram-negative bacteria were between 0.25-2.0% (not effective in highest test-concentration of 4% against *E. coli* and *P. aeruginosa*). MICs against 10 Gram-positive bacteria were between 0.25-2.0%.

In several publication eucalyptus oil of unknown quality was tested. Bosnic et al. (2006) screened the antimicrobial activity of eucalyptus essential oil by a diffusion test against Gram-positive and Gram–negative bacteria (no positive control included). The activity of eucalyptus oil was more pronounced against Gram-positive bacteria than against Gram-negative bacteria with inhibition zones of 12.5/18.0 mm (*S. aureus/B. subtilis*) versus 13.0/10.5 mm (*E. coli/P. aeruginosa*). MICs with broth dilution method were 0.097 mg/ml (*B. subtilis*) and 0.39 mg/ml (*S. aureus, E. coli, P. aeruginosa)*. Chung et al. (2007) found that 100 µl injection of eucalyptus oil in 100 ml nutrient broth suppressed the growth of the cell of *Staphylococcus aureus* at 100% (no positive control included). Hendry et al. (2009) analysed the anti-microbial activity of Chlorhexidine (CHG) and eucalyptus oil against bacteria grown in suspension and biofilm using microbroth dilution and ATP bioluminescence, respectively. Antimicrobial activity was shown for eucalyptus oil against suspensions and biofilm of *S. aureus* (MIC=4 and 256 g/l versus 1 and 128 mg/l for CHG), MRSA (MIC=2 and 512 g/l versus 2 and 128 mg/l for CHG) and *E. coli* (MIC=8 and 16 g/l versus 1 and 16 mg/l for CHG).

Prabuseenivasan *et al*. (2006), using the disc diffusion method, could show that eucalyptus oil (unknown quality) at different concentrations (50 µl diluted 1:1, 1:5, 1:10 and 1:20) failed to inhibit the growth of any tested strains (Gram-negative bacteria such as *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus vulgaris* and Gram-positive bacteria such as *Bacillus subtilis* and *Staphylococcus aureus).*

1,8-cineol

Bosnic *et al*. (2006) and Hendry et al. (2009) screened also the antimicrobial activity of 1.8-cineole in their test systems showing that 1,8-Cineole (unknown concentration) was active against two Gram-positive bacteria (*S. aureus*, *B. subtilis*), while it was inactive against the Gram-negative bacteria *E. coli* and *P. aeruginosa*) and the essential oil was more active then 1,8-cineol.

Assessor´s comments:
Only in vitro experiments were performed with Eucalyptus aetheroleum. The results show in several experiments anti-microbial activity. The concentrations used are relatively high, more than 100 times higher as the concentrations of the positive control in Hendry et al. (2009). For clear effects seen in concentrations of >100 µg/ml a physiological correlation is not plausible. In the

experiments of Prabuseenivasan et al. (2006), eucalyptus oil failed to inhibit the growth of any tested strains.

Antiviral activity

In vivo

1,8-cineole

Li *et al*. (2016) evaluated the effect of 1,8-cineol (30, 60, 120 mg/kg) or oseltamivir (10 mg/kg) on mice infected with influenza A virus. Mice were treated 2 days before viral challenge and received concomitant treatment for 5 days after infection. On day 6 post-infection, 10 mice per group were sacrificed to collect related samples, measure body weight and lung wet weight, and detect the viral load, cytokine, pathological changes, ICAM-1, VCAM-1, and NF-kB expression in the lung. Survival rates and body weight were higher in the oseltamivir-treated mice and in the 1,8-cineol (60 and 120 mg/kg) treated mice than those in the untreated control group. Moreover, 1,8-cineol efficiently decreased the level of IL-4, IL-5, IL-10, and MCP-1 in nasal lavage fluids and the level of IL-1β, IL-6, TNF-α, and IFN-γ in lung tissues of mice infected with influenza virus. The results also showed that 1,8-cineol reduced the expression of NF-kB p65, intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM)-1 in lung tissues.

In vitro

Eucalyptus oil

Schnitzler *et al.* (2001) demonstrated in RC-37 cells using a plaque reduction essay that eucalyptus oil (Ph.Eur.) (0.01%) reduced virus titres by 58-75% for HSV-1 and HSV-2. The IC_{50} for HSV-1 and HSV-2 plaque formation was 0.009% and 0.008% (no positive control included). 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.

In other publication eucalyptus oil of unknown quality was tested. Astani et al. (2010) tested the potential antiviral effect of eucalyptus oil against *Herpes simplex* virus type I (HSV-1) *in vitro* in RC-37 cells using a plaque reduction essay. 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 with essential oil (no positive control included).
Madia *et al.* (2022) describe the antiviral activity of vaporized *Eucalyptus globulus* essential oil against influenza virus type A. The virucidal activity was evaluated by exposing influenza A Puerto Rico 8/H1N1 virus (PR8) to eucalyptus oil for 30 min at 37°C in an incubator at 5% CO_2. The eucalyptus oil reduced viral infection by 78% with no cytotoxicity (no positive control included). It could be shown by negative staining transmission electron microscopy that eucalyptus oil interfere with the lipid bilayer of the viral envelope, leading to the decomposition of membranes.

Single substances (1,8-cineole, α-pinene)

Astani *et al*. (2010) tested the potential antiviral effect of 1,8-cineole and α-pinene against *Herpes simplex* virus type I (HSV-1) *in vitro* in RC-37 cells using a plaque reduction essay. 1,8-Cineole revealed no plaque reduction (IC_{50} of 1200 µg/ml). The potential antiviral effect of α-pinene was determined with an IC_{50} of 4.5 µg/ml (no positive control included).

Assessor´s comments:
Only in vitro experiments were performed with Eucalyptus aetheroleum. Results on anti-viral activity is depending on the methodology and the tested viruses. For example, for herpes virus the IC_{50} could be given with 55 µg/ml for the Eucalyptus oil, no activity was showed against

adenovirus. The clinical relevance is not clear.

Influence on respiratory tract fluid/ciliary beat frequency

In vivo

Eucalyptus oil

Eucalyptus oil of unknown quality was tested. Boyd and Pearson (1946) tested the expectorant properties of eucalyptus oil. 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. Also to guinea pigs eucalyptus oil in doses of 10, 50 and 100 mg/kg body weight was given by stomach tube. In this experiment a control (ethanol 12% with 5 ml/kg) was included.

Table 4: Effect of eucalyptus oil upon output of respiratory tract fluid in Guninea pigs [Boyd and Pearson, 1946]

substance	dose	increase of output on respiratory tract fluid			
		1st hour	2nd hour	3rd hour	4th hour
Eucalyptus oil	10 mg/kg	48%	58%	52%	14%
Eucalyptus oil	50 mg/kg	157%	172%	114%	101%
Eucalyptus oil	100 mg/kg	88%	31%	8%	4%
Ethanol 12%	5 ml/kg	0%	-20%	8%	22%

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; HED=4374 mg/kg). Lower doses had no effect on the volume of RTF.

1,8-cineol

Zänker *et al*. (1980) reported, during inhalation of 300 µmol 1,8-cineole, the lung compliance of anaesthetised rabbits was improved by a factor 0.3. An increase over 300 µmol resulted in a decrease of lung compliance almost to the starting value. No remarkable morphologic change on bronchus epithelium could be observed up to 500 µmol by using scanning electron technique (no positive control included).

In vitro

Eucalyptus oil

Eucalyptus oil of unknown quality was tested in several publications. 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 (no positive control included). Riechelmann et al. (1997) found that eucalyptus oil exposed in a concentration above 6.7 g/m^3 can reduce *in vitro* ciliary activity of human respiratory cells (no positive control included). 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 posology, but can occur, when overdosed. Neher et al. (2008) examined effects of eucalyptus essential oil on the activity of ciliated epithelial brushings of inferior nasal turbinate *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 mg/ml) and remained elevated at 20 min has been observed. 2% eucalyptus oil (~20 mg/ml) resulted in an increase of ciliary beat frequency of 11.8% at 5 min (no positive control included).

1,8-cineol

Zänker *et al*. (1980) investigated the effect of 1,8-cineol on synthetic and pulmonary surfactant layers. Under their experimental conditions, 1,8-cineol exhibited surfactant-like effects, namely a decrease in surface tension between water and air (no positive control included).

Assessor´s comments:
In vitro and in vivo experiments on influence on respiratory tract parameters were performed with eucalyptus oil and 1,8-cineol. In a dose finding study Boyd and Pearson (1946) found a Human Equivalent Dose (HED) = 11 mg/kg (50 kg bw. corresponds to 550 mg Eucalyptus oil in adults) to be maximal effective in augmenting the output of respiratory tract fluid. *The traditional used daily doses reported from member states are between 300-600 mg. A second study in rabbits could not confirm these results. Further in vitro data suggest influence on ciliary beat frequency and surfactant like effect. The clinical relevance is not clear.*

Anti-inflammatory / analgesic / antinociceptive activity activities

In vivo

Eucalyptus oil

Silva *et al.* (2003) demonstrated an anti-inflammatory effect of eucalyptus oil (unknown quality) in the paw oedema test in rats after subcutaneous injection in a dosage of 100 mg/kg (HED = 16 mg/kg). Furthermore, analgesic effects were demonstrated by i.p. injection at doses of 10 or 100 mg/kg (rats, positive control: morphine; HED = 1.6 and 16 mg/kg) most pronounced after 45 min 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).

Akinrinde *et al*. (2019) investigated the potential role of eucalyptus oil (unknown quality) in protecting against aflatoxin B1 (AfB1)-induced gastrointestinal damage in rats. Control rats were administered with the vehicle (1% Tween 80) for 14 days, while two groups were pre-treated with oral doses of eucalyptus oil (50 and 100 mg/kg b.w.) for 14 consecutive days, along with two oral doses of AfB1 (5 mg/kg b.w.) on days 12 and 14. Two other groups were treated with eucalyptus oil alone at the two doses for 14 days. AfB1 administration induced oxidative and inflammatory disturbances and reductions in glutathione peroxidase and superoxide dismutase (SOD) activities. Treatment with eucalyptus oil produced significant improvements in the biochemical parameters as well as the appearance of the gastric and intestinal mucosa (no positive control included).

Zhao *et al*. (2021) evaluated the anti-inflammatory effects of eucalyptus oil (unknown quality) in mice (500, 750, and 1000 mg/kg). Several indicators of inflammation, such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), malondialdehyde (MDA), nitrogen monoxide (NO), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α), urea, creatinine, alanine aminotransferase (ALT), has been screened. In addition, tissue injury was determined by H&E staining. The results revealed that eucalyptus oil suppressed inflammation by decreasing SOD, TNF-α, and NF-κB levels (no positive control included).

Single substances (1,8-cineole, β-pinene)

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. Additionally, 1,8-cineole (oral administration) was tested 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). Dye leakage promoted by acetic acids was reduced in a dosage of 200 und 400 mg/kg.

Liapi *et al*. (2007) examined antinociceptive effects of 1,8-cineole and β-pinene in rats and mice (tail-flick test, hot plate test). A dosage of 0.3 mg 1,8-cineole/kg in rats (i.p.) provoked a significant effect on reaction time in both tests. β-Pinene provoked antinociceptive action in rats only (0.3 mg/kg, i.p.). Morphine (0.75 mg/kg in rats, 1 mg/kg in mice) served as control.

Assessor´s comments:
The in vivo studies for anti-inflammatory and analgesic activities were performed with eucalyptus essential oil. Due to the administration routs (s.c., i.p.) is the clinical relevance not clear. In the in vivo experiments with 1,8 cineole oral doses of 400 or i.p. doses of 0.2-05 mg/kg were applied. The clinical relevance of these studies with doses/application ways cannot be estimated.

Immunomodulatory effects

In vivo

Eucalyptus oil
Serafino *et al*. (2008) administered eucalyptus oil (unknown quality) 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) (no positive control included). 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 a nearly restored phagocytic activity of peripheral blood granulocytes/monocytes.

In vitro

Eucalyptus oil
Eucalyptus oil of unknown quality was tested in two publications. 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-α, INF-γ) was not influenced (no positive control included). 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-α release from LPS-stimulated macrophages was observed with ~1 µg eucalyptus oil/ml (no positive control included).

1,8-cineole
Juergens *et al*. (1998b) analysed immunomodulatory effects *in vitro*. 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 (no positive control included).

Assessor´s comments:
The in vivo study was performed with an oral dose in the dose range of the traditional use. The results hint to immunomodulatory effects in laboratory animals, while the clinical relevance cannot be estimated.

Antitussive effects

In vivo

1,8-cineole

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). With 8 mg/l a reduction in cough frequency could be shown in 54% of the animals and with 2.7 mg/l in 46% of the animals, which lowered the mean values from 10.7 to 8.8/7.8. However, these lower values were not significant different (no positive control included).

Assessor´s comments:
The in vivo data for the antitussive effect were performed with 1,8-cineole via inhalation had no significant effect on cough frequency.

Table 4: Overview of the main non-clinical data/conclusions with p.o. or by inhalation administration

Herbal preparation tested	**Posology**	**Experimental model**	**Reference**	**Main non-clinical conclusions**
Comparable/similar preparations to preparations of the monograph				
Eucalyptus oil (unknown quality)	10, 50 and 100 mg/kg bw; by stomach tube	*in vivo*; guinea pigs; p.o.	Boyd and Pearson (1946)	50 mg/kg maximal effect (172% in 2nd hour) in augmenting the output of respiratory tract fluid
eucalyptus oil (unknown quality)	0.4, 0.5, 1.0, 1.5, 3.0, 4.0, 6.0, 7.5, 9.0, 27, 81, 243, 729, 2187, 6561, 19683 mg/kg/ bw added to the boiling water bath used for inhalation	*in vivo*; rabbits; inhalation	Boyd and Sheppard (1968)	no effect on respiratory tract fluid
eucalyptus oil (unknown quality)	12 mg/kg bw	*in vivo* rats; p.o. for 15 days after bone marrow suppression blood was collected on day 0, 7, 15 and 20	Serafino et al (2008)	day 15 immuno-competent rats: increase of circulating monocytes, of phagocytic activity of granulocytes and monocytes immuno-supressed rats: recovery of the percentage of circulating granulocytes; nearly restored phagocytic activity of peripheral blood granulocytes/monocytes

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
eucalyptus oil (unknown quality)	50 and 100 mg/kg bw	*in vivo* rats; p.o. for 14 days + two oral doses of Aflatoxin B1 (5 mg/kg bw) on days 12 and 14 control group: two oral doses of Aflatoxin B1 (5 mg/kg bw) on days 12 and 14	Akinrinde et al. (2019)	aflatoxin B1 administration induced oxidative and inflammatory disturbances and reductions in glutathione peroxidase and superoxide dismutase (SOD) activities, while treatment improved significantly biochemical parameters as well as appearance of the gastric and intestinal mucosa
eucalyptus oil (unknown quality)	500, 750, and 1000 mg/kg	in ivo mice; p.o. (500, 750, and 1000 mg/kg) for 14 days + LPS (10 mg/kg) i.p. after 6 h of the last administration positive control group: normal saline for 14 days + LPS (10 mg/kg) i.p. after 6 h of the last administration sacrifice at 12 h after LPS administration	Zhao et al. (2021)	eucalyptus oil suppressed inflammation by decreasing SOD, TNF-α, and NF-κB levels
Isolated substances				
1,8-cineol	30, 60, 120 mg/kg oseltamivir (10 mg(kg)	*in vivo* mice, p.o. infected with influenza A virus; treatment started 2 days before	Li et al. (2016)	survival rates + body weight: higher in oseltamivir group and 1,8-cineol (60 and 120 mg/kg) group than those in the untreated control group decreased level of IL-4,

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
		viral challenge and was continued for 5 further days after infection		IL-5, IL-10, and MCP-1 in nasal lavage fluids + level of IL-1β, IL-6, TNF-α, and IFN-γ in lung tissues + reduced expression of NF-kB p65, intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM)-1 in lung tissues
1,8-cineole	100, 200, 400 mg/kg bw (rat paw oedema, formalin + acetic acid test, writhing test) 400 mg/kg bw (cotton pellet granuloma)	*in vivo* rats: rat paw oedema cotton pellet granuloma; p.o. mice: formalin + acetic acid test; p.o. writhing test; p.o.	Santos and Rao (2000)	anti-inflammatory effects: reduction in paw oedema: 100 mg/kg=26% 200 mg/kg=26% 400 mg/kg=46% Indomethacin 5 mg/kg=62% reduction of cotton pellets induced granuloma after 7 days: 400 mg/kg=37% (wet weight) / 40% (dry weight) Indomethacin 5 mg/kg =25% (wet weight) / 55% (dry weight) Inhibition of dye leakage in acetic acid test: 200 mg/kg=35% 400 mg/kg=38% Acetic acid 250 mg/kg=40% antinociceptive effects: inhibition paw licking response in formalin test: 400 mg/kg= significant inhibition of paw licking response at first and second phase (0-5 min+20-25 min) 200 mg/kg=inhibition of paw licking response only at second phase (20-25 min) Reduction of abdominal constrictions responses (writhing movements): 100 mg/kg=48% 200 mg/kg=53% 400 mg/kg=40% Acetylsalicylic acid 250 mg/kg=69%
1,8-cineole	0.8, 2.7, 8 µg/ml	conscious guinea-pigs	Laude et al.	not significant reduction in cough frequency for 2.7

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
	administered by using a vaporising apparatus (constant airflow of 1 ml/min)	cough induced by citric acid	(1994)	and 8 mg/ml

3.1.2. Secondary pharmacodynamics

Several *in vitro*-studies on antioxidant, repellent, antifungal, activities were published. Those *in vitro* studies on secondary pharmacology are not considered relevant for the purpose of establishment of the monograph.

Effects on wound healing

Alam *et al*. (2018) conducted a wound healing study of eucalyptus essential oil (unknown quality) containing nanoemulsion in rats over 24 days. In formulations E1-E5, the concentration of eucalyptus oil varied from 12% to 16%, 20%, 24% and 28% w/w. Optimized nanoemulsion E1 was selected for wound healing study, collagen estimation and histopathological evaluation in rats in comparison with pure eucalyptus oil and standard gentamycin. At day 4 post-wounding, a significant reduction in swelling and exudates in rats treated with the optimized nanoemulsion of eucalyptus oil was recorded. These effects were comparable to standard antibiotic treated rats and higher than control and pure eucalyptus oil. On day 24 post wounding all groups were comparable.

Pulmonary fibrosis

Brinsi et al. (2022) analyzed the protective effect of eucalyptus oil against bleomycin (BLM)-induced pulmonary fibrosis in rats. The control group received no treatment, the BLM group received only intratracheally BLM (2 mg/kg) and the eucalyptus oil group received BLM followed by eucalyptus oil (10 mg/kg). The treatment with eucalyptus oil reversed the deleterious effects of reactive oxygen species and the inflammation raised by BLM. *E. globulus* extracts could improve BLM-induced pulmonary fibrosis.

Convulsant / anti-convulsant properties

In the review article of Bahr *et al*. (2019) the effects of eucalyptus oil (among other essential oils) on epilepsy and acute seizure were assessed. Two main types of animal models emerged in the review: models of acute seizure and models of chronic epilepsy. In the majority of the studies, the essential oils or their isolated compounds were administered via intraperitoneal injection. Although known to produced adverse epileptic reactions in humans and seizures in animals, paradoxically, oils with high 1,8-cineole content have produced some anticonvulsant properties or delayed onset and severity of seizures in animal models with induced seizures. According to the authors one potential explanation for these conflicting results is that 1,8-cineole may be a weak partial $GABA_A$ antagonist. It is possible that 1,8-cineole competes for the same site as other convulsant drugs; however, its effects are much weaker, giving the appearance of anticonvulsant activity. A second mechanism explaining the anticonvulsive action of was given with the capacity of essential oils to block ionic currents.

3.1.3. Safety pharmacology

Hu *et al.* (2014) investigated parameters of safety pharmacology of eucalyptus oil (unknown quality) emulsion in water. Four groups of 10 rats, each containing 5 females and 5 males, consumed a daily dose of 0 (Group II, emulsifier and distilled water), 3% (Group III), 6% (Group IV) and 12% eucalyptus oil emulsion (Group V), respectively. Each rat was smeared in the skin of its back with the dose of 0.3 mL for 5 days. In the safety pharmacology study, administration of eucalyptus oil emulsion did not produce any side effects to rats in nervous system, cardiovascular system and respiratory system.

3.1.4. Pharmacodynamic interactions

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).

Assessor's comments:
The topical use of the eucalyptus oil preparations is not intended with other topical drugs.

3.1.5. Conclusions

Results from relevant experimental studies on eucalyptus oil are limited and not required.

Results of *in vitro* experiments with eucalyptus oil show antimicrobial activity, while single studies also had negative results. Results of antiviral activity was depending on the tested viruses and the methodology. In an *in vivo* dose-finding study, an effect in augmenting the output of respiratory tract fluid could be shown. Further effects such as anti-inflammatory and analgesic could be shown in high doses *in vivo* studies. The quality of the essential oil used was not always described. Also for the main component of the essential oil – 1,8-cineol – a variety of effects were reported in *in vivo* and *in vitro* studies. The clinical relevance of all these studies are not clear.

Results from relevant experimental studies to support the proposed indications are limited, however the reported pharmacological effects are not considered contradictory to the traditional uses in context of cough and cold and localized muscle pain.

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

Absorption

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 was concluded from the results.

Distribution

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).

Metabolism/ Pharmacokinetic interactions with other medicinal products

Jori *et al*. (1969) found 1,8-cineole increased significantly the activity of the microsomal enzyme system in rats. Rats were treated by s.c. 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).

Hohenwallner & Klima (1971) found 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).

Jori et al. (1972) reported, 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.

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).

Madyastha & Chadha (1986) investigated the effect of 1,8-cineole on liver and lung microsomal cytochrome P-450 and b_5 systems of rats. 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.

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.

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 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 seen with IC_{50} values 20-100 µg/ml.

These findings correspond to the results obtained by Miyazawa et al. (2001 a, b), who reported that 1,8-cineole is an effective substrate for CYP3A4 enzymes in rat and human liver microsomes. Duisken et al. (2005) found, that 1,8 cineole is catalyzed by human CYP3A4 and CYP3A5 enzymes. The metabolites can be used as urianary marker for intake of 1,8 cineole.

Assessor's comments:
Eucalyptus oil was found to be in vitro a weak inhibitor of CYP3A4.

Elimination

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 & 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).

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

3.3.1. Single dose 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 [quoting von Skramlik, 1959 & Ohsumi et al., 1984]).

Hu *et al.* (2014) investigated the acute toxicity of eucalyptus oil (unknown quality) emulsion in water. Five experimental groups with 10 rats each, containing an equal number of both male and female, were formed. The five groups were treated orally with the eucalyptus oil emulsion at dose of 2772, 3267, 3960, 4752 and 5742 mg/kg. The animals were observed for gross behavioral neurologic, autonomic and toxic effects for 24 h and then daily for 14 days. The study was performed according to the OECD Guideline 425 ("Up and Down procedure"). In this test, animals were dosed once at a time. If the animal survived, the dose of the next animal was increased; if the animal died, the dose for the next animal was decreased. After treated for 50 min, the rats in the top-dose group appear to move slowly, gather together, extreme sensitivity to noise and convulsion. The rats in the rest groups showed mild symptom and less death. Death necropsy showed a lot of undigested food and EOE in stomach and no tissue damage except for lung and liver. The LD_{50} value of eucalyptus oil emulsion by oral administration was 3811.5 mg/kg determined by Karber's method. In high doses the liver was the target organ of eucalyptus oil emulsion toxicity. The creatinine of high dose group (Group V) and medium dose group (Group IV) were higher than the control group (Group I) indicating eucalyptus oil emulsion could cause damages to the kidney of rats.

Zhao *et al*. (2021) analyzed the acute toxicity of eucalyptus oil (unknwon quality). Mice were randomly divided into 8 groups, with 10 mice in each group, half male and half female. The mice were given 1250, 2500, 3750, and 5000 mg/kg eucalyptus oil by gavage. The survival rate of mice for 2 weeks was observed and recorded. According to the modified Karber's method, the LD_{50} of mice with oral administration of eucalyptus oil was 3065 mg/kg.

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). The LD50 for 1,8-cineole is 2.5 g/kg for rats (Opdyke, 1975).

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.

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

3.3.2. Repeat dose toxicity

Eucalyptus oil

Hu et al. (2014) investigated the subchronic toxicity of eucalyptus oil (unknown quality) emulsion in water. In the thirty-day oral toxicity study, four groups of 10 rats, each containing 5 females and 5 males, consumed a daily dose of 0 (Group II, emulsifier and distilled water), 396 (Group III, 4% eucalyptus oil emulsion), 792 (Group IV, 8% eucalyptus oil emulsion), 1188 (Group V, 12% eucalyptus oil emulsion) mg/kg bw for 30 consecutive days. The animals were monitored for clinical and behavioral symptoms such as diarrhea, immobility and mortality. Results showed that the dose over 792 mg/kg bw may slow down the growth of male rats. The target organs of the toxic effects were the liver, kidney and spleen. The behaviors of rats were not adversely affected up to 1188 mg/kg bw.

1,8-cineole

Kristiansen & Madson (1995) reported 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. Alpha2-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).

De Vincenzi *et al*. (2002) summarised the 28-day toxicity data on 1,8-cineole from National Toxicological Programm (1987). 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.

3.3.3. Genotoxicity

For eucalyptus oil no Guideline-conform test on genotoxicity have been published.

Eucalyptus oil

Miyamoto *et al.* (2009) evaluated the genotoxic potential of *Eucalyptus globulus* oil (unknown quality) 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. 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.

3.3.4. Carcinogenicity

For eucalyptus oil no carcinogenicity studies have been published.

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 bw 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. 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.

3.3.5. Reproductive and developmental toxicity

For eucalyptus oil no Guideline conform studies on reproductive and developmental toxicity have been published.

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 (Pages *et al*., 1990).

1,8-cineole

Jori & Briatico (1973) investigated 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 new born 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.

3.3.6. Local tolerance

Not available.

3.3.7. Other special studies

Not applicable.

3.3.8. Conclusions

Non-clinical information on the safety of eucalyptus oil is scarce. With the limited data available it is difficult to draw any firm conclusions especially regarding genotoxicity, carcinogenicity and

reproductive and developmental toxicity. Investigations on pregnant and lactating rats suggest that 1,8-cineole cannot cross the blood-milk barrier, but is able to penetrate the placenta tissue.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

The following text is included in the monograph section 4.6:
Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.
No fertility data are available.

The following text is included in the monograph section 5.3:
Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on eucalyptus oil and his constituent 1,8- cineol to support the proposed indications are limited and not required.

Specific data on pharmacokinetics and interactions are not available. It was found in *in vitro* studies that eucalyptus oil is a weak inhibitor of CYP3A4.

Non-clinical information on the safety of eucalyptus oil is scarce. In sub-chronic toxicity studies in very high doses the liver and kidney were target organs.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. Investigations on pregnant and lactating rats suggest that 1,8-cineole cannot cross the blood-milk barrier, but is able to penetrate the placenta tissue. As there is no sufficient information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

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

There are no human studies to pharmacodynamics of oral use of eucalyptus oil.

<u>Eucalyptus oil; inhalation</u>
Burrow et al. (1983) investigated the effects of either 1 g of eucalyptus oil 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. 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. The majority of subjects reported a cold sensation and an increase of nasal airflow after administration of eucalyptus oil. The stimulation of nasal cold receptors and the sensation of nasal airflow appears to be of importance for patient comfort in the treatment of nasal congestion.

Choi et al. (2022) investigated the effects of olfactory stimulation with eucalyptus aroma oil on the psychophysiological responses in women, in Korea. The eucalyptus oil was used on 23 women aged between 20 and 60 years. They inhaled the scent for 90 s through a glass funnel attached to their

lab apron, 10 cm below their nose, while the pump was activated. Electroencephalography, blood pressure, and pulse rate were measured before and during inhalation of the aroma oils. Systolic blood pressure significantly decreased after introduction, which indicates stress reduction.

Eucalyptus oil; cutaneous use

Packman & London (1980) induced cough in 32 healthy subjects by citric acid aerosol via a mask, in the single-blind cross over study. Eucalyptus oil in a petrolatum base (no further information) was applied to the chest in a single 7.5 g dose and then massaged for 10-15 seconds. Cough responses are registered by a lateral pressure tap. The eucalyptus oil formulation decreased cough counts from ½ hour through 1 ½ hours. The decrease at the 2 hour challenge was of marginal significance.

1,8-cineole ; oral

Juergens et al. (1998a) analysed anti-inflammatory effects in humans. 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.

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-α, IL-4, IL-5 and IL-8 could be found in physiologic achievable concentrations (10^{-5} M).

1,8 cineole; oral

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. Neither treatment with the herbal product nor with ambroxol had a significant influence on lung function.

After 4 days of oral treatment of 3 x 200 mg 1.8-cineole daily, the ciliary frequency of cilia brushed from the inside of the nose, placed in a nutrient solution and observed under a microscope fitted with a photomultiplier. It increased by 8.2% ($p<0.001$), whereas corresponding increases after placebo treatment were insignificant (1.7% respectively) (ESCOP, 2003 [quoting Kaspar et al., 1994]).

Assessor´s comments:
Human pharmacological data cover the inhalative use of eucalyptus oil and support the plausibility of use in context of nasal congestion in cough and cold. The experiments on the antitussive effect of topical use in artificial induced cough as well as on sedative effects after inhalation have to be assessed as having no clinical relevance. No pharmacological data are available for the oral use of eucalyptus oil in context of cough and topical use in muscle pain.
Human pharmacological data of the 1,8-cineole, the main component of eucalyptus oil, are available for the oral use. They shows anti-inflammatory effects and improvement of 29ucociliary clearance. The data support the plausibility of the traditional use in cough.

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

No pharmacokinetic study has been conducted in special populations as gender, race, weight, impaired hepatic function, impaired renal function, elderly and children. Only data of clinical safety and efficacy studies are available to give some information to dosages of different age groups. The applied daily doses and single doses are in accordance with the posology of the long traditional medicinal use of eucalyptus oil.

Eucalyptus oil
Clinical pharmacokinetic data on eucalyptus oil are not available for oral use, inhalation or cutaneous use.

1,8-cineole; inhalation
In humans (n=10) a plasma half-life of 35.8 minutes was established after a 10-minute inhalation of 1.8 cineole (Römmelt *et al*., 1988).

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.

1,8-cineole; oral use
Zimmermann *et al*. (1995) 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 α-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 un-chewed tablet and within 0.7-1.1 h for the chewed tablet. Absorption was almost 100% (93.2% uncrushed capsule, and 95.6% crushed capsule). Intake of 80 mg 1.8-Cineol resulted in C_{max} plasma level of 69.1 ng/ml (median, uncrushed capsule) and 98.5 ng/ml (median, crushed capsule).

Assessor's comments:
Clinical pharmacokinetic data on eucalyptus oil are not available for oral use, inhalation or cutaneous use.
The results of the single substance 1,8-cineole show that it is well absorbed by inhalation, 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. O*ral 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 un-chewed tablet and within 0.7-1.1 h for the chewed tablet. Absorption was almost 100%.*

4.2. Clinical efficacy

4.2.1. Dose response studies

Classical dose response studies are not available.

4.2.2. Clinical studies (case studies and clinical trials)

Eucalyptus oil

There are no clinical studies with eucalyptus oil available.

1,8-Cineol

Since 1,8-cineol is the main component of eucalyptus oil (according to Ph.Eur. ≥70%) the clinical studies concerning 1,8-cineol are also seen as supportive. Publications before 2000 and in indications not used in Europe are not taken into considerations.

Cai et al. (2020) present in an overview (also including Kehrl *et al*., 2004; Juergens *et al*., 2003; Worth *et al*., 2009; Worth & Dethlefsen, 2012; Fischer & Dethlefsen, 2013) the source, biological activities, mechanisms, and application of 1,8-cineole since 2000. It was concluded that the accumulated evidence suggests that 1,8-cineole is a potential drug for the treatment of respiratory diseases and the therapeutic effects in the clinical trials was seen proven on asthma, COPD, and rhinosinusitis.

In a reference controlled 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 the comparator (Tesche et al., 2008).

Martin et al. (2020) examined in a restrospective cohort study (RWD) for 30 days the relationship between the initial treatment of acute lower and upper tract respiratory infections with phytopharmaceuticals and the duration of the disease, as well as between the initial treatment and the use of antibiotics in the further course of the disease in a. A total of 117,182 patients, who had been prescribed phytopharmaceuticals and an equal number of controls were available for analysis. The majority of study patients were treated by general practitioners (67%) and pediatricians (28%).
The number of prescriptions in the database for 1,8-cineole were 13,685 from general practitioners and 601 from paediatricians.
Phytopharmaceutical prescription on the day of diagnosis was significantly associated with fewer long sick leaves (>7 days: OR 0.92, $p < 0.001$; >10 days: OR 0.88, $p < 0.001$; >14 days: OR 0.84, $p < 0.001$; >18 days: OR 0.82, $p < 0.001$; >21 days: OR 0.83, $p < 0.001$). The effect on a sick leave period of more than 7 days was significant for several phytopharmaceuticals, the strongest associations were found for cineole (OR 0.74 [0.63–0.86]) and the Pelargonium root extract EPs 7630 (OR 0.79 [0.54–0.96]).

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

Clinical studies in special population with eucalyptus oil are not available.

1,8-cineole

Schmidt (2013) performed a non-interventional study in 893 patients aged 4-90 years with acute bronchitis. They were treated with 100 mg 1,8-cineole/capsule for the duration of 8 days. The dosage for children under 10 years of age was 1 capsule three times daily, children 10 years of age and older as well as adults took 2 capsules t.i.d. The age group 4 to 20 years comprised 89 patients (51 female, 38 male). Next to tolerability and compliance the severity of symptoms was

assessed on a five-point rating scale. A reduction of the total symptom score from 7.7 points at baseline to 1.4 points after treatment was observed. Cough as a lead symptom was improved by 95.6 %. In only 0.4 % of patients mild adverse events were observed. No adverse effects were reported in children. 81.4% of patients indicated a distinct improvement of complaints after 3-4 days.

Nauert & Oestreich (2015) reported a non-interventional study to demonstrate compliance, tolerability and clinical course during therapy with 1.8-Cineol in children and infants with acute bronchitis. 336 children (group A: n = 178; 2-7 years; group B: n = 158; 8-11 years) with acute bronchitis were treated with 3 × 100 mg 1.8-Cineol per day for 7-9 days. Main outcome criteria were the assessment of compliance, tolerability and symptom progression (bronchitis symptom sum score, BSS) at baseline (V1), after 4 days (V2) and after 7-9 days (V3) of therapy. Compliance was rated as very good and good by 89% and 79% in both groups (physician and patient, respectively) with slight advantages in group B. Tolerability was rated as very good and good by 93% of both physicians and patients. There were 4 gastrointestinal side effects (nausea, vomitus, diarrhoea) in 3 of 336 patients (0.9%). The BSS improved significantly over the course of therapy from a mean of 8.61 (V1) to 5.09 (V2) and 1.38 (V3). At the end of therapy, 79% of all patients were symptom-free. Both symptom improvement and recovery rate were comparable in both age groups.

4.4. Overall conclusions on clinical pharmacology and efficacy

Human pharmacological data cover the inhalative use of eucalyptus oil and support the plausibility of use stimulating of nasal cold receptors and the sensation of nasal airflow in context of nasal congestion in cough and cold. No pharmacological data are available for the oral and cutaneous use of eucalyptus oil in context of cough and topical use in muscle pain. Human pharmacological data of the 1,8-cineole, are available for the oral use. They show anti-inflammatory effects and improvement of mucocilliary clearance. The data support the plausibility of the traditional use in cough.

No controlled clinical efficacy studies with eucalyptus oil are available to prove a well-established use. Some clinical efficacy studies were conducted with the main constituent of the essential oil, 1,8-cineole. They were conducted orally in different acute and chronical respiratory tract diseases, as cough in acute and chronic bronchitis and asthma bronchiale. The posology used in the clinical studies is orally, daily 600-800 mg 1,8-cineole, corresponding 860-1140 mg eucalyptus oil (calculated with 70%). These studies cannot proof efficacy for the essential oil, but support the traditional medicinal uses in context of cough in different respiratory tract infections.

5. Clinical Safety/Pharmacovigilance

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

Eucalyptus essential oil

Higgins et al. (2015) reviewed patch testing data at the Skin and Cancer Foundation over the period January 1993 and December 2013. There were 596 patients patch tested with 5% eucalyptus oil of 8334 patients patch tested over this period. They identified 2 positive reactions (0.34% of those tested). The authors concluded the allergic contact dermatitis in eucalyptus oil is rare in literature but do occur.

1,8-cineole

Kehrl et al. (2004) studied the efficacy and safety of 1,8-cineole capsules compared 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. No differences have been found for parameters of leukocyte count and erythrocyte sedimentation rate. Mild side effects were observed in the verum group. Heartburn and exanthema were assessed as related to the medication. Tension headache, ear pain, epistaxis, and a torsion of the foot, were considered as not related to the medication. No adverse events occurred in the placebo group.

In the clinical study Worth et al. (2009) 1,8 cineole (3x200 mg daily) was given. In 22 patients, side effects were seen. In 17 cases adverse events were not related to study medication. In the placebo group 11 cases were not related to the study medication, and two cases of heartburn were related to the study medication. In the verum group 6 cases were reported as not related to the study medication. In 3 patients the adverse events nausea, diarrhoea, and heartburn was reported as related to 1,8-cineole.

Fischer & Dethlefsen (2013) conducted a clinical study of 242 patients with confirmed acute bronchitis. Over a period of 10 days, all patients were administered 3 x 200 mg of 1,8-cineole, or a respective placebo, per day. A safety examination was carried out on all patients, who were administered the study medication. Within the placebo group, it was assumed that two of the recognised and recorded adverse events (e.g. gastrointestinal infection) were not related to the study medication, whereas a further AE was interpreted as being related to an intolerance of the study medication (i.e. heartburn and burning mouth). During treatment with1,8-cineole 3 adverse events were reported as not being related to the study medication (otitis and sinusitis, eye burning, headache). In one case, a patient complained of stomach-aches, which was interpreted as being related to the study medication. The difference between the two treatment groups was neither clinically relevant, nor statistically significant.

In the reference-controlled trial Wittmann *et al.* (1998) in 29 patients, adverse events considered treatment related in the 1,8-cineole group were headache with eye burning and stomach ache in one patient each compared to two cases of exanthema in the ambroxol group.

Table 6: Clinical safety data from clinical trials with 1.8-Cineol

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
Improvement of lung function Wittmann et al. (1998)	randomised double-blind, cross-over	verum: 1,8-cineole 3 x 200 mg/day Control: ambroxol (3 x 30 mg/day) one week	29 patients patients = >20 years	patients with COPD	verum: 1 x headache with eye burning and 1 x stomach ache related to study medication control: to two cases of exanthema related to control	
Efficacy study Kehrl et al. (2004)	prospective, randomized, placebo-controlled, double-blind	verum 1,8-cineole 3x 200 mg daily placebo 7 days	verum n=75 placebo n=75 patients = 18-57 years	patients with acute non purulent rhinosinusitis	verum: heartburn (from day 5) and exanthema (from day 4) (no numbers given) related to the study medication placebo: no adverse events	no statistically relevant differences according to the authors
Efficacy in concomitant therapy Worth et al. (2009)	placebo-controlled, double-blind	verum: 1,8-cineole 3 x 200 mg daily placebo 6 month, during winter time	verum n=110 placebo n=110 patients = 40-80 years	patients with COPD as concomitant therapy	verum: 3 adverse events (nausea, diarrhoea, heartburn) related to study medication placebo: two cases of heartburn related to placebo	no clinically relevant or statistically significant difference between groups
Efficacy study Fischer & Dethlefsen (2013)	placebo-controlled, double-blind	verum: 1,8-cineole 3 x 200 mg daily placebo 10 days	verum n=121 placebo n=121 patients = 18-70 years	Patients with acute bronchitis	verum: 1x stomach ache related to study medication placebo: 1 x heartburn and burning mouth related to placebo	no clinically relevant or statistically significant difference between groups

5.2. Patient exposure

There is no information available on the extent of eucalyptus oil use in the general population. Aside from market presence from eucalyptus oil there are no concrete data concerning patient exposure from medicinal products.

1,8-cineole

The main food sources are eucalyptus oil (up to 80% 1,8 cineole), the herbs and spices mugwort, sweet basil, rosemary, sage and cardamom and their essential oils. Highest exposure from food is likely to arise from hard (cough) candy in which up to about 130 mg 1,8 cineole /kg or about 2000 mg eucalyptus oil/kg have been reported to be used (SCF, 2002; quoting Fenaroli, 1995). Consumption of 10 g of hard candy containing 2000 mg eucalyptus oil/kg would result in an intake of up to 16 mg of 1,8-cineol, equivalent to 0.27 mg/kg bw for an adult of 60 kg. A mean daily intake of 1,8-cineol from flavoured foodstuffs in France has been estimated to be 4.5 mg/person, equivalent to 0.075 mg/kg bw (SCF, 2002). Maximum concentrations of 1,8-cineol in cosmetic products have been reported to be 0.4% in soap, 0.04% in detergents, 0.1% in creams and lotions and 1.6% in perfume (SCF, 2002; quoting Opdyke, 1975).

5.3. Adverse events, serious adverse events and deaths

Information from the labelling of traditional used preparations:

From the licenced preparations side effects as nausea, vomiting and diarrhoea are mentioned after ingestion of eucalyptus oil preparations and hyposensitivity reactions are known.

Information from monographs

Side effects are given with nausea, vomiting and diarrhoea (in rare cases) in Commission E monograph (Blumenthal et al., 1998) and German standard marketing authorisation (Standardzulassung, 1996).

Safety information from meta-analyses and review reports

Gardiner et al. (2013) perform a systematic review of the comprehensiveness of reporting of published case reports of adverse events associated with use of herbal products in the pediatric population. Ninety-six unique journal papers were identified and represented 128 cases. Of the 128 cases, 37% occurred in children under 2 years old, 38% between the ages of 2 and 8 years old, and 23% between the ages of 9 and 18 years old. Twenty-nine percent of cases were the result of an intentional ingestion while 36% were from an unintentional ingestion. Only 41% documented the plant part. Dosage information revealed 59% of cases reported. The most frequent herb mentioned in case reports was eucalyptus (n = 12) (nor further differentiation between herb, essential oil or 1,8-cineole).

Assessor´s comments:
The data to adverse reactions were not distinguished to eucalyptus oil or the constituent 1,8- cineole, nor to oral, inhalation or topical use. The authors did not asses the cases related to eucalyptus oil. From the report, it is not clear what product and dose was used.

Douros et al. (2016) analysed herb-induced liver injury in a case-control surveillance study. Potential cases of liver injury were ascertained in more than 180 departments of all 51 hospitals in Berlin (Germany). Among other phototherapeutic preparations, *Eucalyptus globulus* induced hepatotoxicity has been investigated. In nine cases the association was assessed as possible, one case also for *Eucalyptus globulus* (no information on preparation and dose; concomitant use with clarithromycin and multivitamins of unknown dose and composition; ALT/ULN 6.1; AST/ULN 3.1; ALP/ULN 0.4; Bilirubin 0.5 mg/dL; no coagulopathy; hepatitis A, B, C viruses negative, other viruses missing; clinical symptoms: fatigue; no jaundice, no acholic faeces, no dark urine, no abdominal pain, no signs of

hypersensivity; no liver failure; infectious aetiology was not ruled out; normalization after secession of the drugs in 30 days). Regarding the potentially hepatotoxic effects for *Eucalyptus globulus*, the existing literature is limited. The authors analysed the missing information and concluded, finally, despite the existence of preclinical data implicating a hepatotoxic potential for the main compound of *Eucalyptus globulus*, 1,8-cineole, there are no cases of liver damage in association with its use.

Assessor's comments:
In the preclinical toxicological studies, effects on the liver were seen in very high doses. In the case reported by Douros et al. (2016) the information on the product and dose is missing. No adequate information on the dose and composition of the concomitant preparations (clarithromycin, multivitamin) is given. The information on the cases does not support a hepatoxic potential for eucalyptus oil.

In a review article Bahr et al. (2019) summarized case reports of eucalyptus oil and other essential oils rich in 1,8-cineole content with regard to convulsant activity. No human case of eucalyptus oil mono preparation is listed in the review, but with 1,8-cineole or combinations of essential oils including eucalyptus oil.

Galan et al. (2020) reviewed the available pre-clinical and clinical data on Eucalyptus oil and 1,8-cineole. Side effects of nausea, exanthema and diarrhoea were reported in clinical trials with 1,8-cineole. The broader literature has identified other rare but possible adverse effects including contact allergy and skin reaction and vocal cord dysfunction. Ingestion of large doses can lead to CNS depression, abnormal respiration as well as epigastric pain. Collapse of cardiovascular system and seizures has also been reported. Pharmacokinetik interaction with other drugs such as aminopyrine, have been described in animal studies as well as in studies on volunteers. Doses up to 600 mg/day were considered by the authors as safe based on clinical research.

Assessor´s comments:
The data to adverse reactions were not distinguished to eucalyptus oil versus 1,8- cineole. As no clinical studies were performed with eucalyptus oil, it seems that all the results are from studies with 1,8 cineole. Gastrointestinal disorders such as abdominal pain, nausea, vomiting and diarrhoea as well as immune system disorders such as allergic reactions are given in the monograph in chapter 4.8 Undesirable effects.

Oral and/or cutaneous use and/or inhalation

A series of publications concerning adverse reactions were published.
Mathew et al. (2017) identified 10 cases of eucalyptus oil-induced seizure (EOIS) by five neurologists in three tertiary care hospitals in India during the period of two years from January 2015 to December 2016. Among 350 cases of acute symptomatic seizures per year, EOIS was seen in 5 patients, giving an annual incidence of 1.4%. The mean age of the cohort was 22.3 years (range 2–45 years). All patients were males. Eight out of 10 patients inhaled steam of water mixed with eucalyptus oil, 1 patient used eucalyptus oil as intranasal drops, and 1 patient used eucalyptus oil as massage oil. Seizures developed at an average of 4.1 min (range 2–10 min) after exposure to eucalyptus oil. Eight patients had generalized tonic-clonic seizure, and 2 had complex partial seizure. Ictal phase lasted for a few seconds to a few minutes. The mean duration of the postictal phase was 45 minutes.
Mathew et al. (2021b) performed a multi-center prospective study, conducted in four hospitals over four major hospitals, in south India, from October 2014 to March 2018. Every person presenting with the first episode of seizure or breakthrough seizure was asked about exposure to essential oils, mode of exposure, time to onset of a seizure in relationship to exposure, duration of seizure, type of seizure, and antiepileptic drug therapy. During the four-year period there were 55 patients with essential oil-

related seizure (EORS). 22(40%) had essential oil-induced seizures (EOIS) and 33(60%) had essential oil-provoked seizures (EOPS). The female: male ratio was 1:1.1, the age of the patients ranged from 8 months to 77 years. In the EOIS group, 95% had generalized tonic-clonic seizures and 5% had focal impaired awareness seizures. In the EOPS group, 42.4% had focal impaired awareness seizures, 27.3% generalized tonic-clonic seizures, 15% focal to bilateral tonic-clonic seizures, and 15% focal aware motor seizures. Essential oils implicated were preparations containing eucalyptus and camphor: from the EOIS group (n=22) 18%% were induced by mono eucalyptus oil preparations, from the EOPS group (n=33) 24% were induced by mono eucalyptus oil preparations.
Bandi et al. (2021) performed a case record review, with cases of seizures related to eucalyptus oil having been evaluated between December, 2018 and June, 2019 at a tertiary care paediatric Center in Southern India. A total of 15 children (8 girls) met the inclusion criteria, with median (range) age of 4.8 years (6 months-14 years) – 10 were younger than 5 years. The preparations are available as over-the-counter medications. The most commonly used preparation was a liquid formulation Zinda Tilismath; menthol plus was locally applied for one child and eucalyptus oil ingestion in one child. For Zinda Tilismath, drinking after dilution with water was the commonest mode of exposure (n=10), while three children had local application as well. Its ingredients include eucalyptus oil, camphor, menthol, thymol and alkanet root as mentioned in the package insert. One child was exposed to herbal balm with similar composition. The quantity of the liquid preparation used was 2-5 drops (6 of 13 children) and 0.5-2.0 ml (6 of 13 children). One child drank 5 ml of the preparation. In the study, the amount of preparation taken had no correlation with either onset of seizures or duration of seizures (excluding status epilepticus).
Dudipala et al. (2021) identified three case repots of paediatric patients with eucalyptus oil-induced seizure in India. A 3-year old boy developed generalized tonic clonic seizures after ingestion of 10 drops of eucalyptus oil with milk. A 4-year old boy developed vomiting and seizure 15 minutes after ingestion of an unknown amount of eucalyptus oil. A 7-year old girl developed generalized tonic clonic seizures after ingestion of 1 ml of eucalyptus oil with milk.

Assessor´s comments:
Several cases of adverse events of seizures are available from literature. The information on the cases is not complete.
The reports reflect to over-the-counter sales products with unclear (controlled) quality. It is reported from Ittyachen et al. (2019) that in Indian "eucalyptus oil" products used by patients delivered to hospitals due to overdosages, camphor was detected. That point to "fake eucalyptus oil", prepared from the cineole fraction of camphor laurel. Therefore, it is unclear, if also the quality of the products is responsible for the adverse case reactions. Similar cases are not reported from licenced preparations in Europa.
Furthermore, often the reports are not connected to eucalyptus oil mono-preparation, but multi-combination/ preparation (ingredients include also e.g. camphor and/or menthol, thymol).
The use in children is not accepted in the HMPC-monograph for oral eucalyptus oil. No conclusions can be drawn from the information available.

A case report described the occurrence of a lozenge-induced esophagitis in a women after the ingestion of 15 to 20 tablets containing sugar, corn syrup, citric acid, food colorants and flavours (cherry, menthol, and eucalyptus oil) one hour before surgery (Sharara, 2000).

Vocal cord dysfunction precipitated by eucalyptus inhalation was observed in a woman (Huggins et al., 2004).

Cutaneous use

Patch testing showed a positive reaction in a 53-year-old patient suffering from relapsing eczema after

applying Eucalyptus oil 2% (Schaller & Korting, 1995).

A case report by Shishir et al. (2011) described the occurrence of oral mucosa injury caused by topical application of Eucalyptus oil to the gums.

Gyldenløve et al. (2014) reported allergic contact dermatitis in a 51-year-old female florist, working with eucalyptus plants. In the patch test, positive reaction was seen to eucalyptus stem and leaf but not eucalyptus oil 2%.

De Groot & Schmidt (2015) published eight reports on allergic contact dermatitis caused by eucalyptus oil and Mathew et al. (2017) identified a case of eucalyptus oil induced seizure by massage oil.

Use as bath additive

An unusual case was reported by Burkhard et al. (1999). 12-month-old healthy girl was given five prolonged baths containing an unknown quantity of essential oils of eucalyptus, pine, and thyme over a 4-day period for a benign and afebrile upper respiratory tract infection. Shortly after the last bath she became agitated, drowsy and had a tonic convulsion lasting for 1 min. Two identical episodes occurred the same day. On admission to hospital, neurological examination was normal, as were all blood tests, CSF analysis, brain computed tomography, and magnetic resonance imaging. Viral cultures were negative. EEG showed bursts of spikes at the anterior leads which became occasionally generalized. Over the following days the number of seizures increased dramatically to a maximum of 133 in 24 h, occurring in clusters especially during sleep. Phenobarbital, phenytoin, valproate, carbamazepine, clonazepam, clobazam and nitrazepam were used, either alone or in various combinations, without any improvement. After 4 weeks the seizure activity decreased suddenly and stopped while she was being treated with phenobarbital and phenytoin. After recovery her EEG improved markedly but still showed bilateral temporal spikes, more prominent on the right side.
The child’s development was subsequently marked by a temporary delay in her psychomotor and speech abilities. At 21, 28, and 32 months of age she again suffered from a cluster of identical tonic seizures, each time triggered by febrile infections. Repeated EEGs, CSF analysis, and cerebral magnetic resonance imaging were normal. Another afebrile convulsive event occurred at the age of 5 years.
The authors assumed that the subsequent recurrence of seizures despite no further use of essential oils and the development of cognitive disturbances suggest that the child had an underlying epileptogenic encephalopathy and it was hypothesised that exposure to EOs initiated epileptic events that would have evolved into a less dramatic course had these substances not been used.

Intranasal use

Serious toxicity symptoms (irritable mucous membranes, tachycardia, dyspnoea, nausea, vomiting, muscular weakness, drowsiness and coma) have been observed in children following nasal application of 1,8-cineole (Santos & Rao, 1997).

Kamal et al. (2015) reported a case of lipoid pneumonia due to intranasal application of a product containing 1.2% eucalyptus oil, 4.8% camphor and 2.6% menthol for the past twenty years.

Assessors´s comments:
The nasal application is not part of the HMPC monograph. The use in children is not recommended.

Eudravigilance database

In the Eudravigilance database for the period 01.01.2013 to 01.03.2023, 80 spontaneous reports of suspected adverse drug reactions associated with eucalyptus oil were reported. The selectes active substance was »EUCALYPTUS, EUCALYPTUS OIL, EUCALYPTUS RADIATA ESSENTIAL OIL«. The report type was »objects from the list, spontaneous, other, not available to sender, report from studies.«. The

medical product characterisation was »suspect, interacting«.

49 case reports were related to products with eucalyptus oil as a single active ingredient and no intake of concomitant products. Out of these 49 cases, there were 4 serious case reports where the reactions were related to hypersensitivity, including one anaphylatic shock in a 9-year-old child using a bath additative, a 4-year-old child that developed dysphagia, dyspnoe/difficult breath and seizure using a bath additative, and one report with incomplete information after oral use. The fourth serious case report where the reactions was related to hypersensitivity, the product was used for dissolving old root canal filling materials. The majority of non-serious case reports were reported (when specified) after oral use of eucalyptus oil and a few after cutaneous use or inhalation. The non-serious case reports are reflecting adverse reactions listed in the product information for products on the market i.e. gastrointestinal disorders and reactions related to hypersensitivity (e.g., immune system disorders).

Assessor's comments:
Published reviews, pharmacovigilance data from products of eucalyptus oleum preparations already on the market, and monographs related to safety are congruent, show that gastrointestinal reactions (as heart burn, nausea, vomiting, diarrhea), immune system disorders (allergic reactons including severe allergic reactions) and skin and subcutaneous tissue disorders (contact eczema) can occure.
Frequencies of adverse reactions cannot be stated according to the convention laid down in the SmPC guideline, as no clinical studies with eucalyptus oil are available. Frequencies from clinical studies with the component 1,8 cineole cannot be transferred completely to eucalyptus oil.
Eucalyptus oil should be used with caution in inflamed and ulcerated conditions of the gastrointestinal tract. Knowing this fact, the marketed /licenced capsules are factoried gastroresistent. The essential oil drops should be admitted with a glass of water.

All uses: Immune system disorders
Not known frequency: allergic reactions including severe allergic reactions as systemic allergic reactions.

Oral use: Gastrointestinal disorders
Not known frequency: gastrointestinal reactions (as heart burn, abdominal pain, nausea, vomiting, diarrhoea).

Cutaneous use: skin and subcutaneous tissue disorders
Not known frequency: contact eczema

5.4. Laboratory findings

No data are available on eucalyptus oil.

5.5. Safety in special populations and situations

Elderly
Vieira et al. (2020) investigated the acute effect of eucalyptus essential oil in cardiovascular responses of rest and after isometric resistance exercise (IRE). Twenty elderly individuals, after being submitted to experimental sessions with inhalation of eucalyptus oil or control condition, remained in recovery for 60 min (Rec-60') and then performed three sets of 1 min (1 min recovery between sets) in IRE, for dominant upper limb in handgrip, with intensity of 30% of maximum voluntary contraction (IRE-30%). There were no differences ($p>0.05$) when comparing the sessions (eucalyptus oil vs. control) in Rec-60' and IRE- 30%. Differences were found in the time factor of rest to Rec-60' in HR and RRi variables

and of rest to IRE-30% in systolic BP, diastolic BP and RPP. Inhalation of eucalyptus oil did not provided significant changes in cardiovascular and autonomic responses on rest and after IRE-30% in elderly individuals.

Patients with impaired renal or liver function
In literature (ESCOP, 2003; WHO, 2002, Commission E, 1986) the use of eucalyptus oil is absolute contraindicated in cases of inflammation of the gastrointestinal tract, the gall bladder and impaired liver function.

Douros et al. (2016) reported in a clinical study human case reports on liver toxicity based of different preparations, including eucalyptus aetheroleum. The authors concluded, despite the existence of preclinical data implicating a hepatotoxic potential for the main compound of *Eucalyptus globulus* 1,8-cineole, there are no cases of liver damage in association with its use.

Altogether no adequate clinical studies are available in patients with renal and/or hepatic impairment.

Local tolerance

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 applied amounts of ointment applied have not been reported.

5.5.1. Use in children and adolescents

No data from clinical efficacy or safety studies in children are available for the essential oil. The use in children can only be concluded from the medicinal use of the marketed products.

Oral use:
The oral use in children under 12 years of age is not recommended in the HMPC monograph due to lack of adequate data. This is in in accordance with the historical data and marketed preparations.

Inhalation (drops in hot water):
The nasal mucosa is an autonomic reflexogenic organ, which has a remote action to the heart, lungs and circulation and may lead to sudden apnoea and glottal constriction. Children less than 2 years old particularly present this reflex, so all the substances with a strong odour (for instance essential oils, particularly observed for menthol and camphor) could lead to a closure of glottis in infants (Kratschmer-Reflex) and must be avoided (Dost and Leiber, 1967; Jorch, 2009).
According the "Guideline on pharmaceutical development of medicines for paediatric use" (EMA/CHMP/QWP/805880/2012 Rev. 2), in generally the patient acceptability and age appropriateness of orally inhaled paediatric medicines needs to be justified. Caution is necessary in inhalations with hot water, to avoid burns, for all age groups. The area of the eyes should be outside of the steam.
Regarding the lack of historical data and the safety aspects of hot water inhalations, the use is not recommended in children under 3 years for the HMPC monograph.

Cutaneous use:
The historical data show, that the use of ointments is generally licenced in marketed products from 2 years of age. This is in accordance with the literature.
Due to the cooling effect and strong odour, eucalyptus oil and ointments thereof, should not be applied to or near the face of babies and very young children (Blumenthal et al., 1998) because of the risk of reflex spasm of the glottis. Therefore, the usage in children below the age of 2 years is contraindicated.

The HMPC considered the use in children under 3 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.

Use as bath additive:
The use as bath additive is generally recommended from 2 years in marketed product. The HMPC considered the use in children under 3 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.

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. In the licenced 1,8-cineole preparations an absolute contraindication is given for the oral use in children under 12 years of age. Safety data from oral use of 1,8-cineole are considered supportive.

In 2012 CHMP published an Assessment report for suppositories containing terpenic derivatives (CHMP, 2012). It was pointed out that the clinical evidence shows that children less than 30 months are more prone to neurological disorders due to immaturity of the central nervous system, which results in a higher susceptibility to neurological toxicity. It was also pointed out that suppositories are known to distribute systemically, due to product absorption through the rectal mucous membrane which is particularly vascularised. The CHMP therefore concluded that the use of suppositories containing terpenic derivatives should be contraindicated in children less than 30 months, as well as in children with a history of epilepsy or febrile convulsion and in children with a recent history of anorectal lesion. Suppositories are not covered by the HMPC monograph.

5.5.2. Contraindications

According information from monographs and literature (Blumenthal et al., 2000, Standardzulassung, 1996) the oral use is contraindicated in diseases of the gastrointestinal tract and bile ducts, and sever liver disease/the liver function is impaired. Externally, eucalyptus preparations should not be applied to the face, especially the nose, of infants and young children. A contraindication for this age group is not formulated.

There are products on the market (ointments and bath additives) for more than 30 years, which are authorised starting with the age group of children from 2 years of age, while smaller age groups are contraindicated.

As in other HMPC monograph on essential oils the use in children under 24 months of age is contraindicated because there is a risk that 1,8-cineole containing preparations, like other essential oils, can induce laryngospasm. The use in children with history of seizures (febrile or not) is contraindicated in the HMPC monograph.

The HMPC monograph Community herbal monograph on *Eucalyptus globulus* Labill., Eucalyptus polybractea R.T. Baker and/or *Eucalyptus smithii* R.T. Baker, etheroleum (EMA/HMPC/307781/2012) gives the information:
The use of eucalyptus oil is contraindicated in hypersensitivity to Eucalyptus oil or 1,8-cineol, in children with history of seizures (febrile or not).
The use in children under 24 months of age is contraindicated because there is a risk that 1,8-cineole containing preparations, like other essential oils, 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.

5.5.3. Special warnings and precautions for us

Indication 1: Traditional herbal medicinal product used for relief of cough associated with cold.

When dyspnoea, fever or purulent sputum occurs, a doctor or a qualified health care practitioner should be consulted. If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Oral use
The use in children under 12 years of age has not been established due to lack of adequate data.
Eucalyptus oil should be used with caution in inflamed and ulcerated conditions of the gastrointestinal tract.

Inhalation
The use in children under 12 years of age has not been established due to lack of adequate data.
Caution is necessary in inhalations with hot water, to avoid burns. The area of the eyes should be outside of the steam.

Cutaneous use and use as bath additive
The use in children between 2 and 3 years of age has not been established due to lack of adequate data.
Eye contact with unwashed hands after the application of eucalyptus oil /use of the preparation may potentially cause irritation.
Eucalyptus oil should not be applied on broken or irritated skin.

Indication 2: Traditional herbal medicinal product used for the symptomatic relief of localised muscle pain, after serious conditions have been excluded by a medical doctor.

When reddening or swelling of the aching parts occur a doctor or a qualified health care practitioner should be consulted. If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Cutaneous use and use as bath additive
The use in children between 2 and 3 years of age has not been established due to lack of adequate data.
Eye contact with unwashed hands after the application of eucalyptus oil /use of the preparation may potentially cause irritation.
Eucalyptus oil should not be applied on broken or irritated skin.

5.5.4. Drug interactions and other forms of interaction

No clinical studies on drug interactions of eucalyptus oil are available.

1,8-cineol
Jori et al. (1970) reported that in an experimental clinical study in five healthy human volunteers that received aerosolized 1,8-cineol for 10 min for 10 consecutive days an increase in plasma clearance of aminopyrine (600 mg) was observed in 4 of 5 participants. All drugs were administered 24 h after the last aerosolization and the authors conclude that 1,8-cineole is likely a hepatic cytochrome P450 inducer, even when given via the inhalation route. The plasma of controls was 7.2±1.1 and of treated persons 4.9±0.4 (µg/ml) aminopyrine (68% of the normal untreated) Pharmacokinetic-based drug interaction via CYP induction or inhibition warrants further study.

Assessor´s comments:
1,8-cineole (40% w/v in olive oil) was emulsified 1:1 with distilled water and 2 ml of such an emulsion was nebulized. The tested eucalyptus oil dose contains [calculated] 400 mg cineole. The dose corresponds to app. 533 mg eucalyptus oil (calculation based on 75% cineole). The reduction of the plasma level corresponds app. 32%. However, the methodology is not state of the art, as no information on the AUC is given. Inducers of CYP3A should be classified based on the effect on oral midazolam clearance or plasma AUC. A ≤ 50%, > 50 - ≤ 80% and > 80% reduction in midazolam AUC after oral administration classifies an investigational drug as mild, moderate and strong inducer, respectively. No conclusion can be drawn from one-point measurement of aminopyrine.

Information from monographs (as ESCOP, 2003; Blumenthal et al., 2000; WHO, 2002) states, that eucalyptus oil induces in animal studies the enzyme system of the liver involved in the detoxification process. Therefore, the effects of other drugs can be weakened and or shortened.

Boyle and Walters (2011) published probable and clinically relevant interaction between warfarin and the popular cough lozenges 'Fisherman's Friends' in a 67-year-old man. The ingestion of these lozenges for approximately 1 month was associated with a significant reduction in international normalised ratio to subtherapeutic levels. The INR remained stable after ceasing the lozenges. 'Fisherman's friend' are a popular brand of cough lozenges worldwide, retailing in over 100 countries and selling over 500 000 packets of lozenges per day. Each lozenge contains, among other ingredients, eucalyptus oil, menthol and liquorice each of which has a theoretical potential of interacting with drugs metabolised by Cytochrom P450 and therefore warfarin.

Assessor´s comments:
No adequate clinical studies on drug interactions of eucalyptus oil are available. An experimental human study with cineole hint to possible induction of P450. Contrary, the in vitro-results of Unger and Frank (2004) hint to inhibition of CYP3A4, even though IC_{50} were recorded in very high concentrations compared to plasma concentration measured in human studies. The clinical relevance for eucalyptus oil is not clear, therefore no information was included in the monograph.
The case report of Boyle and Walters (2011) reports an interaction of a combination product containing eucalyptus oil with warfarin, what is a drug, which is metabolized mainly through the enzyme CYP2C9 not CYP3A4.

5.5.5. Fertility, pregnancy and lactation

There are no studies with eucalyptus oil

1,8-cineole
Kirsch et al. (2012) investigated time-dependent aroma changes in human milk after intake of an odorant-containing pharmaceutical preparation by correlating sensory evaluation with quantitative results. Human milk donors ingested 100 mg of encapsulated 1,8-cineole. 21 milk samples from 12 nursing mothers (19 weeks to 19 months postpartum) underwent sensory analysis, of which 14 samples were quantified by stable isotope dilution assay (SIDA) analysis. Furthermore, several consecutive breast milk and exhaled breath gas samples from one volunteer after intake of 1,8-cineole were analysed by proton-transfer-reaction mass spectrometry (PTR-MS) and sensory evaluation on three separate days. The emergence of the characteristic eucalyptus-like odour of 1,8-cineole in exhaled breath after capsule ingestion coincided with its transfer into milk; its presence in breath was therefore used to indicate the time at which milk should be expressed for gathering samples. Odorant transfer could not be confirmed by sensory analysis in 7 of the 21 milk samples, most likely due to disadvantageous timing of milk expression. The other 14 samples exhibited a distinct eucalyptus-like odour. Quantitative results matched these observations with <20 mcg/kg 1,8-cineole in the odourless

samples and 70 to an estimated 2090 mcg/kg 1,8-cineole in the other samples. In one woman who donated 3 samples, the highest concentration of 71 mcg/kg occurred at 1.5 hours after ingestion, with concentrations of 1 mcg/kg before ingestion and 15 mcg/kg at 9.5 hours after ingestion. It was concluded by the authors that the transfer of 1,8-cineole into human milk after oral intake is time dependent and exhibits large inter and intra-individual differences.
Although instructed not to, 12 mothers breastfed their infants during the experiment. Mothers reported that none of their infants refused their milk or breastfed less than usual.

The study of Kirsch & Buettner (2013) aimed to characterise the metabolites of 1,8-cineole, identified in human milk, after the oral intake of 100 mg of this substance. Special emphasis was placed on the enantiomeric composition of the metabolites. The volatile fraction of the human milk samples was therefore isolated via Solvent Assisted Flavour Evaporation (SAFE) and subjected to gas chromatography-mass spectrometry (GC-MS). The absolute concentrations of each metabolite were determined by matrix calibration with an internal standard, and the ratios of enantiomers were analysed on chiral capillaries. The concentrations varied over a broad range, from traces in the upper ng/kg region up to 40 mcg/kg milk, with the exception of the main metabolite α2-hydroxy-1,8-cineole that showed concentrations of 100–250 mcg/kg. Also, large inter- and intra-individual variations were recorded for the enantiomers, with nearly enantiomerically pure α2-hydroxy- and 3-oxo-1,8-cineole, while all other metabolites showed ratios of ~30:70 to 80:20.

In a further study Kirsch et al. (2013) investigated the metabolite profiles of 1,8-cineole in human milk after lactating mothers ingested a non-prescription pharmaceutical containing this substance. Ten different metabolites were identified, five of which have been already described in humans and other mammals, three of the metabolites have hitherto only been found in microorganisms and insects (2-oxo-1,8-cineole, 3-oxo-1,8-cineole, 2,3-dehydro-1,8-cineole) and the derivatives a2,3-epoxy-1,8-cineole and 4-hydroxy-1,8-cineole have never before been identified as metabolites of 1,8-cineole. Metabolism profiles showed large inter- and intra-individual differences and were strongly related to sampling time. Identification and relative quantification of the metabolites were accomplished by gas chromatography–mass spectrometry (GC–MS) after preparation of the human milk extracts by solvent assisted flavour evaporation (SAFE). Synthesised reference substances were used to confirm the chemical identity of the detected substances.

In the study of Debong et al. (2021) Eighteen nursing mothers who were nursing their infants of 8 to 53 weeks of age were served a curry dished containing an average of 394 mcg of 1,8-cineole. Baseline 1,8-cineole concentrations in milk averaged 1.44 mcg/l (range 0.07 to 7.57 mcg/l). Milk samples contained 1,8-cineole in concentrations of 0.19 to 7.41 mcg/l at 1 hour after eating, 0.33 to 7.86 mcg/l at 2 hours after eating and 0.22 to 3.33 mcg/l at 3 hours after eating. The authors concluded that ingestion of a customary curry dish can lead to an alteration of the milk aroma, which might be perceived by the infant during breastfeeding and it was demonstrated that the extent of aroma transfer differs between both substances and individuals.

While in the embryotox-database of the Pharmacovigilance and Advisory Center for Embryonal Toxicology at Charité-Universitätsmedizin Berlin (embryotox, 2023) no entry for eucalyptus oil or 1,8-cineol exits, it is very generaly reported, that essential oils can lead to breastfeeding problems by changing the taste of the milk.

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

No fertility data available.

5.5.6. Overdose

Oral use

Gurr & Scroggie (1965) suggested detailed management of poisoning due to eucalyptus and similar volatile oils. Observation for up to four hours after ingestion is indicated, even if sequelae appear mild or absent. Amongst others, attempts to induce emesis are best avoided in infants or if the conscious state is depressed. If the patient is conscious and ingestion of large amount (4 ml for infant, 15 ml for an adult) is presumed, induced emesis in an adult or older child and lavage in an infant or toddler should be considered.

The SCF (2002 [quoting Webb & Pitt, 1993]) summarized, accidental intoxications have been reported following ingestion of eucalyptus oil. The lowest lethal doses reported were 4-5 ml in adults and 1.9 g eucalyptus oil in a 10 year old boy. In other cases, however, ingestion of higher doses caused less severe effects or was even asymptomatic.

Saller et al. (1988) cited a lethal dose for adults of only 4-5 ml eucalyptus oil.

Spoerke (1998) reported signs and symptoms in 14 cases of eucalyptus oil reviewed in a retrospective analyses of Rocky Mountain Poison Centre records during 1987. Inhalation (3 cases), and skin exposure (2 cases) produced no or minimal signs of symptoms, that were treated at home. Ingestions of a "swallow" or more, (5 ml-20 ml; age 7, 8, 20, 20 month, 6, 8, 16, 28 years), gastrointestinal symptoms seemed to be the most common, followed by central nervous system depression. Apnoea was noted only in one child.

Darben et al. (1998) reported occurrence of death from CNS depression after ingestion of 30 ml oil.

Anpalahan (1997) reported a case of suicide attempt in a 73-year-old female. She had consumed an over a half bottle (>190 ml) of eucalyptus oil. She improved over 48 hours. The main complication was pneumonitis and aspiration for seven weeks. Three month later, she died of pneumonia, confirmed by autopsy.

De Vincenzi et al. (2002) listed adverse case reports from ingested eucalyptus oil in amounts ranged from 1 ml to 220 ml. After dialysis two patients survived despite 21-220 ml ingestion, while 2 patients died after an ingestion of only 3.5-5 ml.

Young et al. (2017) reported of a 34-year-old Bangladeshi woman residing in Australia presented after a deliberate ingestion of 600–1000 mL of eucalyptus oil with suicidal intent. Her Glasgow Coma Scale was 3/15, with miosis and unrecordable blood pressure. She regained consciousness and was extubated successfully on day 15.

Ittyachen et al. (2019) reported the cases of two patients (in India), both adults and living in the same room, who unintentionally consumed eucalyptus oil and developed seizures. Eucalyptus oil was taken around 15 ml, supposed for abdominal pain. The authors detected Camphor in the "eucalyptus oil" that the patients had consumed.

Hume et al. (2019) reported a massive eucalyptus oil overdose leading to prolonged coma. A 53-year-old Caucasian man was brought to hospital by ambulance unconscious following intentional ingestion of approximately 500 ml of 100% eucalyptus oil. The patient's Glasgow Coma Score was three. He made a complete neurological recovery.

Mathew et al. (2021a) reported from an observational study conducted in a tertiary care hospital in south India from January 2018 to December 2019. There were 3 young adults with essential oil-related status epilepticus. Two had de novo generalized tonic–clonic status epilepticus, and 1 with posttraumatic occipital lobe epilepsy had focal-impaired awareness status epilepticus. The first 2 cases presented with histories of overdose ingestion of eucalyptus oil (one case 1 tea spoon of 5 ml; second

case 2-3 teaspoons (10-15 ml) eucalyptus oil. The third case had focal impaired awareness status epilepticus after topical application of various balms containing eucalyptus and camphor (no further information on composition and dose of the combination product.

Assessors comments:
From the reports there are no information on the products or the quality of the eucalyptus oil involved. From Ittyachen et al. (2019) it was shown, that adulterations are possible.

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 after accidental ingestion of eucalyptus oil. Additional investigations of 27 patients (aged 0.5-72 months; medically poisoned) showed 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.

Kumar et al. (2015) reported a case of a 6-year-old boy presented with status epilepticus within 10 min of accidental ingestion of 10 ml of Eucalyptus oil. The child improved tremendously within 20 h and was discharged. Another 3-year-old boy presented with status epilepticus within 10 min of accidental ingestion of 5 ml of Eucalyptus oil. The child improved and was discharged. The adverse reactions were considered serious.

Sitaraman & Rao (2019) reported a female infant aged 17 months was admitted to Aashlok Hospital after having accidentally ingested approximately 0.5 ml of store-bought eucalyptus oil. The child exhibited symptoms of drowsiness but no seizures, and her heart rate and respiratory rates were 140 beats/minute and 40/minute respectively. The authors concluded, owing to the wide range of outcomes observed upon ingestion of eucalyptus oil, the lack of standardization preventing meaningful comparison between different preparations available in the (Indian) market, it is probably better to avoid ingesting, to prevent accidental ingestion.

Assessor´s comment:
The lowest amount of 1.7 ml (~1,700 mg) is more than the 8-fold amount of the single dose recommended for adults and adolescents.

The children under 24 months of age is contraindicated. The oral use in children under 12 years is not recommended in the HMPC-monograph.

Topical use
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 topical application (bandages soaked with eucalyptus oil) 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.

Assessor's comment
The following information is given in the HMPC monograph:
Intake of doses larger than those recommended can provoke gastro-intestinal symptoms (abdominal pain, vomiting, diarrhoea, nausea); respiratory problems, apnoea, central nervous depression or loss of consciousness and convulsions; ataxia and other CNS problems, constricted pupils.
Accidental overdose of liniments or bath preparations may cause skin irritation.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been performed.

1,8-cineole
Application of 1,8-cineole, compared to control group, decreased the reaction time. Moreover, subjects in the 1,8-cineole group reported an increased feeling of relaxation when compared with control (Göbel et al., 1994).

Ilmberger et al. (2001) reported in a clinical study 10 or 100 µl 1,8-cineole, applied to a surgical mask, exerted a positive effect on human attention as assessed by measuring motor and reaction times in a reaction time task. Both the experimental group and the corresponding control group (water) consists of 20 healthy human subjects aged between 16 and 67 years. The within-group analysis mainly did not reach statistical significance. The authors concluded the effects on attentional behaviour are mainly psychological.

Assessor's comment:
The relevance of results showing decreased reaction time and contradictory positive effect on reaction time is not clear.

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

Eucalyptus oil is traditionally use for relief of cough associated with cold and for the symptomatic relief of localised muscle pain. No clinical safety studies with eucalyptus oil in the relevant indications and preparations are available.

The use in children under 24 months of age is contraindicated because there is a risk that 1,8-cineole containing preparations, like other essential oils, can induce laryngospasm. The use in children with history of seizures (febrile or not) is contraindicated.
The oral use and inhalation is not recommended in children under 12 years of age. For the cutaneous use and use as bath additive, the use in children between 2 and 3 years of age is not recommended.

Caution is necessary in inhalations with hot water, to avoid burns. The area of the eyes should be outside of the steam.

Eye contact with unwashed hands after the application of eucalyptus oil /use of the preparation may potentially cause irritation.

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

Eucalyptus oil should be used with caution in inflamed and ulcerated conditions of the gastrointestinal tract. The marketed /licenced capsules are gastro-resistant, the same is recommended for new approvals.

The duration of use should be no longer as one week in context of cough and cold and two weeks for topical use in muscle pain in self-medication.

Adverse effects are: for all usages hypersensitivity reactions, including severe allergic reactions (as urticaria, contact dermatitis, irritated mucous membranes of the nose, systemic allergic reactions), can occur. From the oral use gastrointestinal reactions (as nausea, vomiting, and diarrhoea) are reported. The frequency is not known.

Overdose can provoke gastro-intestinal symptoms (abdominal pain, vomiting, diarrhoea, nausea),

respiratory problems (apnoea, tachypnoea), depression or loss of consciousness and convulsions, ataxia and other CNS problems, dilated or constricted pupils.
Accidental overdose of liniments or bath preparations may cause skin irritation.
Treatment is symptomatic.

No adequate clinical studies on drug interactions of eucalyptus oil are available. The drug interaction data are inconclusive from preclinical assessment to case reports. Therefore, in the monograph it is declared, that no interactions are reported.

The local tolerance of topical preparations as ointments and bath additives should be assessed individually in application procedures, since skin reactions following topical application can result also from the vehicle.

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. Adequate tests on reproductive toxicity have not been performed. Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. No fertility data are available.

Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

On the basis of the information on its traditional use, eucalyptus oil proves not to be harmful in the specified conditions of use of the recommended indications and preparations.

6. Overall conclusions (benefit-risk assessment)

Efficacy

There is sufficient evidence for the traditional medicinal use in Europe for Eucalyptus aetheroleum preparations. The following preparations fulfil the requirement of at least 30 years (including at least 15 years with the Community) according to Directive 2001/83/EC as amended, in the pharmaceutical forms:

1) Herbal preparations in solid dosage forms for oral use (gastro-resistant capsules).
2) Herbal preparations in liquid dosage forms for inhalation and cutaneous use (pure essential oil as drops).
3) Herbal preparations in semi-solid dosage forms for cutaneous use (ointments).
4) Herbal preparations in liquid dosage forms as bath additives.

No controlled clinical studies with eucalyptus oil are available to prove a well-established use in Europa. Eucalyptus oil preparations included in the HMPC monograph have been traditionally used in Europe for more than 30 years in the indications "for relief of cough associated with cold" (oral use, inhalation, cutaneous use, bath additive) and "for the symptomatic relief of localised muscle pain" (cutaneous use, bath additive). Corresponding monographs and diverse scientific literature demonstrate plausibility for the traditional used indications and posologies.

Clinical trials are conducted in related indications with oral 1,8-cineole, the main constituent of the essential oil (at least 70% content). They cannot proof efficacy for the eucalyptus oil, but support the plausibility of efficacy in traditional medicinal uses of the eucalyptus oil in context of symptoms of cough in different respiratory tract infections.

Based on medicinal products authorised or registered in the EU the traditional use (oral, inhalation) is

acceptable for adolescents, adults and elderly with indications:

1) Traditional herbal medicinal product used for relief of cough associated with cold

2) Traditional herbal medicinal product used for the symptomatic relief of localised muscle pain.

The cutaneous use and use as bath additive is acceptable from children of the age of 3years, adolescents, adults and elderly in the above mentioned indications.

Safety

The use of eucalyptus oil is contraindicated in hypersensitivity to Eucalyptus oil or 1,8-cineol, and in children with history of seizures (febrile or not).

The use in children under 24 months of age is contraindicated because there is a risk that 1,8-cineole containing preparations, like other essential oils, can induce laryngospasm.

The main safety issue in normal doses are hypersensitivity reactions, including severe allergic reactions (as urticaria, contact dermatitis, irritated mucous membranes of the nose, systemic allergic reactions) and from oral use, gastrointestinal reactions (as nausea, vomiting, and diarrhoea). Eucalyptus oil should be used with caution in inflamed and ulcerated conditions of the gastrointestinal tract.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. No fertility are data available.

Interactions with other medicinal products and other forms of interaction are not reported.

The duration of use should be no longer as one week in context of cough and cold and two weeks for topical use in muscle pain in self-medication.

The intended indications are adequate for the use in self-medication. The efficacy for the oral use, inhalation, cutaneous use and as bath additive is plausible. The safety information in the monograph is adequate to exclude possible risks for special user groups.

A European Union list entry is not supported due to lack of adequate data on genotoxicity for all preparations.

Annex

List of references