Advisory Committee on Plant Preparations

Review of essential oils in capsules

***Rosmarinus officinalis* L.**

1. Botanical Identification

Salvia rosmarinus Schleid.[1,2,3, 38]
Family: *Lamiaceae*
(Drew, B.T. & al. (2017). Salvia united: The greatest good for the greatest number. Taxon 66: 133-145.)

NL : Rozemarijn
FR : Romarin, Romarin officinal, Herbe aux couronnes (regional), Encensier (regional)

Main Synonyms :
Rosmarinus officinalis L.
Rosmarinus angustifolius Mill.
Rosmarinus aunieri Gand.
Rosmarinus communis Bubani
Rosmarinus latifolius Mill.
Rosmarinus rigidus Jord. & Fourr.

Salvia officinalis L. is not a synonym of *Salvia rosmarinus* Schleid.

2. Used plant part

Rosmarinus officinalis is on list 3 of the Royal Decree of 29 August 1997, with the additional mention: “Only the use of the following plant parts is permitted: aerial parts”.

3. Production method

Aerial parts of plant can be used for the preparation of essential oil (E.O.).
This advice is valid for the E.O. prepared from *Rosmarinus officinalis* L., by steam distillation

4. Official monograph reference

Rosmarinus officinalis L. aetheroleum is described in :

- AFNOR - NF ISO 1342: October 2012 Oil of Rosemary, Morroco & Tunisian type - Spanish type
- European Pharmacopoeia : 01/2008 :1846 (Essential oil : 2 types) – 01/2008:1560 (Cut dried leaf).

5. Status in other regulation

The essential oil of *Rosmarinus officinalis* L. is not considered as novel in food supplements (NOT NFS) and therefore falls outside the scope of Regulation (EU) 2015/2283 on novel foods

6. Quantitative and qualitative composition

The composition of the different essential oils of *Rosmarinus officinalis* clearly shows great variability.

Two chemotypes are the subject of a standard ISO 1342:2000(F):

Component	Tunisia and Morocco type		Spanish type	
	Minimum %	Maximum %	Minimum %	Maximum %
α-Pinene	9	14	18	26
Camphene	2,5	6	8	13
β-Pinene	4	9	2	5
Myrcene	1	2	2,5	4,5
Limonene	1,5	4	2,5	5,5
Cineole-1,8	38	55	17	25
p-Cymene	0,5	2,5	1	2
Camphor	5	15	12,5	22
Bornyl acetate	0,1	1,6	0,4	2,5
α-Terpineol	1	2,5	1	3,5
Borneol	1	5	2	4,5
Verbenone	n.d.[a]	0,4	0,7	2,5
[a] n.d. = not detectable				
NOTE : The chromatographic profile is normative and should be distinguished from the typical chromatograms given for information in appendix A .				

The same chemotypes are described in European Pharmacopoeia (Ph. Eur.) 10th Edition

Component	Morocco & Tunisia Type		Spanish Type	
	Minimum %	Maximum %	Minimum %	Maximum %
α-Pinene	9	14	18	26
Camphene	2,5	6	8	12
β-Pinene	4	9	2	6
Myrcene	1	2	1,5	5
Limonene	1,5	4	2,5	5
Cineole-1,8	38	55	16	25
p-Cymene	0,8	2,5	1	2,2
Camphor	5	15	13	21
Bornyl acetate	0,1	1,5	0,5	2,5
α-Terpineol	1	2,6	1	3,5
Borneol	1,5	5	2	4,5
Verbenone	n.d.[a]	0,4	0,7	2,5
[a] n.d. = not detectable				

Tisserand & Young distinguish other minor chemotypes described in the specialized literature:

- Borneol type[4] :
  α-pinene 8,3%, camphene 3,1%, cineole-1,8 20%, p-cymene 1,8%, camphor 15,3%, bornyl acetate 4,9%, α-terpineol 2%, borneol 15,0%, verbenone 8,4%, linalool 3,5%, β-carophyllene 2,2%, terpinene-4-ol 1%, ar-curcumene 1,3%, 1-nonanol 1,2%

- Bornyl acetate type[5] (Mediterranean) :
  α-pinene 24-28,5%, camphene 5,9-7%, cineolee1,8 6,8-13,6%, camphor 9,9-10,4%, bornyl acetate 11,5-14,3%, α-terpineol 2%, borneol 5-8,4%, verbenone 4,3-5,7%, …

- Verbenone type[6] (Egyptian):
  α-pinene 2,5-9,3%, camphene 1,6-3,7%, cineole-1,8 >9%, camphor 11,3-14,9%, bornyl acetate 2-7,6%, α-terpineol 2%, borneol 0,3-1,7%, verbenone 7,6-12,3%, linalool 5,4-6,6% …

- Lawrence (1995a) cites also a β-myrcene type[7]

Camphor is a cyclic monoterpene ketone that is bornane, bearing an oxo substituent at position 2. A naturally occurring monoterpenoid. It has a role as a plant metabolite[8]. Camphor oil has anti-inflammatory and analgesic properties and is used for its aromatic properties, as an insect repellant, in embalming fluids, and in various topical skin preparations.

Most of the chemotypes described do not have reference standards and are likely to exhibit significant compositional variability.

Analysis of the oil of certain origins and some chemotypes may reveal the presence of estragole (> 0.1%), isopinocamphone (up to 2.9% for the verbenone[5] chemotype), pulegone, or e-methyleugenol (> 0 , 1%)

Rosmarinus officinalis L. aetheroleum also appears in the EFSA[9] compendium where the following is mentioned:
"***Rosmarinus officinalis*** L. *Lamiaceae* (*Labiatae*) Aerial Part – Essential oil from the herb: bicyclic monoterpenes: e.g. camphor and monoterpene etheroxide: 1,8-cineole (13 to 31%)
Essential oil from the leaf: monoterpene etheroxide: 1,8-cineole (11.2-47%) and bicyclic monoterpenes: e.g. camphor (13-31%) and monocyclic monoterpene ketone: pulegone (0.98%)."

7. Traditional use

7.1 Historical use

From the 1960s, Dr Jean Valnet, one of the pioneers of the use of essential oils in herbal medicine in France, advocated a time-limited oral dose of 3 drops, 3 times a day [37].

7.2 More recent and current use in the EU

Oral use[40] :

Traditional herbal medicinal product for symptomatic relief of dyspepsia and mild spasmodic disorders of the gastrointestinal tract.

Posology: Adults, elderly, 2 drops daily

If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Contraindications : Hypersensitivity to the active substance.

Obstruction of bile duct, cholangitis, liver disease, gallstones and any other biliary disorders that require medical supervision and advice.

Traditional warnings and precautions for use : The use in children and adolescents under 18 years of age is not recommended due to lack of adequate data[40].

If symptoms worsen during the use of the medicinal product, a doctor or a qualified health practitioner should be consulted.

Cutaneous use & use as bath additive[40]

Traditional herbal medicinal product as an adjuvant in the relief of minor muscular and articular pain and in minor peripheral circulatory disorders.

The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.

Cutaneous use 6-10 % in semi-solid and liquid dosage forms, 2-3 times daily Use as bath additive 10-27 mg per liter, one bath every 2 to 3 days The use in children and adolescents under 18 years of age is not recommended.

If the symptoms persist longer than 4 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

8. Stability / degradation products

For α & β-pinene : Risk of formation of sensitizing peroxides on autoxidation.

9. Kinetics – Metabolism [13, 14]

Rosemary oil: In mice, inhalation of 0.5 ml of volatile oil released into the breathing air resulted in detectable levels of 1,8-cineole in the blood and was biphasic, with a short half-life of about 45 min during a second phase, indicating elimination by a two compartment model [19].

Camphor exerts an analgesic action when applied topically by producing a warm sensation. It excites and desensitizes sensory nerves by activating heat-sensitive TRP vanilloid subtype 1 (TRPV1) and TRPV3 receptors. (S)-camphor is reported to exert a weaker action on TRPV1 channels, which is thought to be a result of tachyphylaxis, which is the reduction of the response to multiple stimulations[11].

Metabolism

(S)-camphor undergoes rapid oxidation to 5-exo-hydroxyfenchone, which is predominantly mediated by human liver microsomal cytochrome (P450). CYP2A6 is the major enzyme involved in the hydroxylation of (-S)-camphor by human liver microsomes[12].

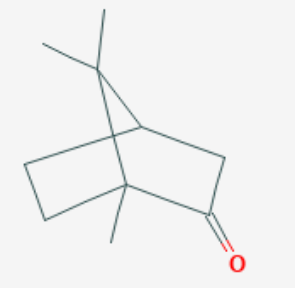
Route of elimination : Camphor undergoes renal excretion [15].

Half-life: Following oral ingestion of 200 mg camphor, the half-life was 167 minutes [15].

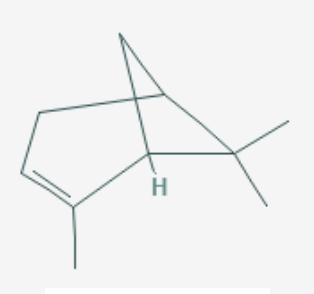
Alpha-pinene: The main metabolic pathways are hydratation, hydroxylation, rearrangement, and acetylation. Five metabolites were identified [16].

The urinary excretion of verbenols after inhalation of alpha-pinene enantiomers was studied. Healthy male subjects were exposed to 10, 225, or 450 mg/cu m (+)alpha-pinene or 450 mg/cu m (-)alpha-pinene for 2 hr while performing light exercise. Exhaled air samples were collected after exposure, and urine samples were obtained before and after pinene exposure. Respiratory elimination of both pinenes was similar; at a concentration of 450 mg/cu m, 7.7% of the total uptake of (+)alpha-pinene and 7.5% of the total uptake of (-)alpha-pinene was eliminated. Urinary excretion of verbenol 4 hours after exposure to (+)alpha-pinene ranged from 1.7% at 450 mg/cu m to 3.8% at a dose of 10 mg/cu m. Urinary excretion of (-)alpha-pinene was similar. A semilogarithmic plot of the excretion data suggested the existence of more than one rate constant for the elimination of (+)alpha-pinene and (-)alpha-pinene. Most of the verbenols were eliminated within 20 hours after a 2 hour exposure. The renal excretion of unchanged alpha-pinene was less than 0.001%. The determination of urinary verbenols may be useful as a biological exposure index for exposure to terpenes [17].

Biological half-life : Half times for elimination of inhaled (+)-alpha-pinene from the blood during the three phases were 4.8, 39, and 695 minutes. Elimination half times of (-)-alpha-pinene were 5.6, 40, and 555 minutes ... [18].



Camphor



Alpha-pinene

10. Overview toxicological data

10.1 General

Tisserand & Young (2014)[5] : Safety summary EO *Rosmarinus officinalis* L.

May be neurotoxic, based on camphor content

Contraindications for 1,8-cineole chemotype (CT): Do not apply to or near the face of infants or children.

Maximal use levels* :
- Camphor CT: dermal maximum: 16.5%, daily adult oral maximum: 513 mg
- α-Pinene CT : dermal maximum: 22%, daily adult oral maximum: 676 mg
- Verbenone CT : dermal maximum: 6.5%, daily adult oral maximum: 192 mg

*Data based on
- camphor dermal limit of 4.5% & oral limit of 2 mg/Kg/day
- isopinocamphone (verbenone CT) dermal limit of 0.24% & oral limit of 0.1 mg/Kg/day

ECHA : Rosemary oil [20]
Danger! According to the classification provided by companies to ECHA in CLP notifications this substance may be fatal if swallowed and enters airways, is very toxic to aquatic life with long lasting effects, is very toxic to aquatic life, is a flammable liquid and vapor, may cause damage to organs, is suspected of causing genetic defects, causes serious eye irritation, may cause an allergic skin reaction, causes skin irritation and may cause respiratory irritation.

Compendium of Botanicals reported to contain naturally occurring substances of possible concern for Human health when used in Food and food supplements [9] :

Essential oil from the herb : bicyclic monoterpenes : e.g. camphor and monoterpene etheroxide: 1,8-cineole (13-31%)

Essential oil from the leaf: monoterpene etheroxide: 1,8-cineole(11.2 – 47%), bicyclic monoterpenes: e.g. camphor (13 – 31%) and monocyclic monoterpene ketone: pulegone (0 – 0.98%)

10.2 Acute toxicity

10.2.1. Acute toxicity E.O. *Rosmarinus officinalis* (totum)

Overview of LD50 values for the entire essential oil

Animals and administration route	LD50 values	Reference
Rat, p.o.	5 mL/kg	Tisserand & Young[5]

Human :

Rosemary oil was not significantly cytotoxic to cultured human umbilical vein endothelial cells [22]

10.2.2. Acute toxicity for camphor

Overview of LD50 values camphor [21]

Animals and administration route	**Toxicity / LD50**	**Reference**
Oral / Mouse	1310 mg/Kg	PubChem June2018 [21]
Intraperitoneal/mouse	3000 mg/Kg	PubChem June2018 [21]
Intraperitoneal/rat	Lowest Published LD 3500 mg/Kg	2012 in PubChem [21]
Subcutaneous/ rat	LD50 : 70 mg/kg	PubChem June2018 [21]

Human :

Age, sexe	**Toxicity / Dose**	**Reference**
Oral/infant	lowest published lethal dose: 70 mg/kg	PubChem June2018 [21]
Oral/child	lowest published toxic dose: 51 mg/kg	PubChem June2018 [21]

10.2.3. Acute toxicity for alpha-pinene

Overview of LD50 values alpha-pinene [23]

Animals and administration route	**LD50 values (mg/kg bw)**
Rabbits, transdermal	> 5000
Rats, oral	3700

Values for humans:

A dose of 15 ml can be fatal for a child. The average lethal dose for an adult ranges from 113 to 170 ml.

10.2.4. Acute toxicity for 1,8-cineole

Overview of LD50 values 1,8-cineole [24]

Animals and administration route	**Toxicity / values LD50**	**Reference**
Rats Male, oral route	4700 mg/kg	European Chemicals Agency (ECHA), 2015 [24]
Rats Female, oral route	4300 mg/kg	European Chemicals Agency (ECHA), 2015 [24]
Rats & Mice	2400 mg/kg	De Vincenzi et al. 2002 [25]

Human :
Low oral toxicity according to some source (Baker 1960) but 1 mL has caused transient coma.
Recovery has occurred after ingestion of 30 mL.
Poisoning produces severe gastrointestinal and CNS effects.

10.2.5 Other constituents with possible health concern

Some rare distillation may contain small amounts of terpenes of health concern:

- Estragole
- Pinocamphone or isomer
- Methyleugenol
- Pulegone

10.3 (Sub)Chronic toxicity

10.3.1. (Sub)chronic toxicity for E.O. *Rosmarinus officinalis* (totum)

No data found

10.3.2. (Sub)chronic toxicity for camphor[21]

Animals and administration route	**Toxicity**		
Oral/rat, Multiple Dose	lowest published toxic dose: 12500 mg/kg/10D- intermittent	Nutritional and Gross Metabolic: Weight loss or decreased weight gain No NOAEL established	2012[21]
Oral/rat, Multiple Dose	lowest published toxic dose: 8000 mg/kg/10D- intermittent	Liver: Changes in liver weight; Nutritional and Gross Metabolic: Weight loss or decreased weight gain	2012[21]

Human : no (sub-)chronic data found

10.3.3. (Sub)chronic toxicity for alpha-pinene[26]

Animals and administration route	**NOAEL-value (mg/kg/day)**	**LOAEL-value (mg/kg/day)**
Rats male, inhalation	21	42
Rats female, inhalation	170	340
Rats male, inhalation	72	144
Rats female, inhalation	72	144

10.3.4. (Sub)chronic toxicity for 1,8-cineole [24]

Animals and administration route	**NOAEL-value (mg/kg/day)**	**Reference**
Wistar Han:RccHan:WIST strain rats, Male & Female – Oral route -	600 mg/Kg/D 28 days	(ECHA); Registered substances, Cineole (January 2015)[24]
Wistar rats, Male & Female	**LOAEL-VALUE** 500 mg/kg/day 50 days	Caldas GF. Et al, 2016 [27]

10.4 Genotoxicity

10.4.1. Genotoxicity for E.O. *Rosmarinus officinalis*

Antimutagenic in Swiss mice / hepatoprotective in rats for *Rosmarinus officinalis* L. bornyl acetate CT.

Animals and administration route	**Antimutagenic dose**		
Swiss mice – oral administration	1100 mg/kg/day 7 days	This dose prevented the formation of micronuclei	Fahim et al, 1999 [5]
Swiss mice – oral administration	1000 or 2000 mg/kg/day	Significant increase of micronuclei but no genotoxicity on 300 mg/kg/day	Tisserand & Young, 2014 [5]

10.4.2 Genotoxicity of camphor [21]

Animals and administration route	**Antimutagenic dose**		
Ames test S. typhimurium TA97a, TA98, TA100, TA102 with and without S9	2500 µg/plate	Negative	Gomes-Carneiro M.R. et al., 1998[28]

10.4.3 Genotoxicity of alpha-pinene [26]

There is no indication that α-pinene is mutagenic.

Animals and administration route	**Antimutagenic dose**		
Ames test S. typhimurium TA97a, TA98, TA100, TA 1535 with and without S9	5000 µg/plate	Negative	Gomes-Carneiro M.R. et al., 2005 [29]
Ames test (pre- incubation method at 37°C for 20 min) Escherichia coli strain WP2 uvrA/pKM101	5 to 10000 µg/ml	Negative	National Tox. program, 2016, [30]

10.4.4 Genotoxicity of 1,8-cineole [24]

There is no indication that 1,8-cineole is mutagenic.

Animals and administration route	**Antimutagenic dose**		
Ames test S. typhimurium TA97a, TA98, TA100, TA102 with and	2500 µg/plate	Negative	Gomes-Carneiro M.R. et al., 1998 [28]
Ames test S. Typhimurium TA98 hisD3052 rfa ΔuvrBbio-/pKM101, TA100 hisG46rfa bio-/pKM101 & TA102 hisG428/pAQ1 rfa/pKM101 with and without S9	5000 µg/ml	Negative	Vuković-Gačić B. et al., 2006 [33]
Sister chromatid exchange Chinese hamster ovary cells (CHO K1)	78.7 micromole	Negative	Sasaki Y-F. et al, 1989 [32]

10.5 Carcinogenicity:

10.5.1 Carcinogenicity of E.O. *Rosmarinus officinalis*

Age, sexe	**Toxicity / Dose**	**Reference**
Human Liver cancer (HepG2) cells	Induce apoptosis	Wei et al. 2008 [31]

10.5.2 Carcinogenicity of camphor

No evidence of carcinogenicity has been found in human tests (ACGIH.1986 ; Monograph of UKPID (Camphor)[44]).

A4; Not classifiable as a human carcinogen. /Camphor, synthetic[45].

10.5.3 Carcinogenicity of alpha-pinene

There is no indication that α-pinene is carcinogenic [26].

10.5.4 Carcinogenicity of 1,8-cineole [5]:

There is no indication that 1,8-cineole is carcinogenic [5].

1,8-cineole showed moderate in vitro cytotoxic activity against five human cell lines: CTVR-1, MOLT-4 (leukemia), K562 (myeloneous leukemia), HeLa (cervical adenocarcinoma) and HepG2 (hepatocellular carcinoma) with IC50 values ranging from 0.1-6.7 g/L after 24 hours incubation [34].

10.6 Reproductive toxicity

10.6.1. Reprotoxicity of E.O. *Rosmarinus officinalis* (totum)

No data found.

The low reproductive toxicity of camphor, alpha-pinene, 1,8-cineole, beta-myrcene and d-limonene suggest that most rosemary oils are not hazardous in pregnancy. However, bornyl acetate and verbenone have not been studied [5].

10.6.2. Reprotoxicity of camphor

Animals and administration route	**NOAEL-value (mg/kg/day)**	**Reference**
Pregnant rats 0, 100, 400 or 800 mg/Kg Gestational days 6-15	800 mg/Kg/day	National Toxicology Program 1992a [35]
Pregnant rabbits 0,50,200 or 400 mg/Kg Gestational days 6-19	400 mg/Kg/day 60% maternal mortality at 500 mg/kg/day	National Toxicology Program 1992a [35]

10.6.3. Reprotoxicity of alpha-pinene [26].

Animals and administration route	**Results**
Mouses, tube feeding	- NOAEL = 560 mg of the mixture/kg daily (mother and fetus)*
Hamsters, tube feeding	- NOAEL = 600 mg of the mixture/kg daily (mother and fetus)*
Rats, tube feeding	- NOAEL = 260 mg of the mixture/kg daily (mother and fetus)*

(*) These studies were performed with a mixture of 85-90% terpenes and less than 10% oxygenated terpenes. The mixture contains 20-25% α-pinene, 15-18% β-pinene and 38-42% sabinene.

10.6.4. Reprotoxicity of 1,8 cineole :

Animals and administration route	Results	Reference
MFC-7 cells In vitro	No estrogenic activity	Nielsen 2008 in Tisserand & Young [5]
Female rat tissue Ex vivo	Did not bind with estrogen receptors	Blair et al. 2000 in Tisserand & Young [5]
Pregnant rodents	NOAEL : 101 mg/kg/10 days (sc) 500 mg/Kg/4 days : fetotoxic (sc) 682 mg/kg/18 days (ip) : maternally & feto-toxic	Tisserand & Young [5]

10.7 Other(s)

10.7.1 *Rosmarinus officinalis* L. aetheroleum (totum)

Animals and administration route	Results	Reference
Normal rabbits 25 mg/Kg (im)	increase plasma glucose level	Al-Hader et al 1994[39]
Male rats 0,5% in daily diet during 2 weeks	Selectively induced CYP2B1 and CYP2B2	Tisserand & Young [5]

The analyzes of several essential oils of rosemary show a possible presence of substances of concern for human health in food and food supplements: estragole, methyleugenol, pinocamphone or its isomers, pulegone.

10.7.2 Camphor

Camphor is known to present a risk of neurotoxicity during an acute exposure (convulsion, seizures) [5]
The gestational rat NOAEL was 100 mg/kg/day (Geller, et al. 1984)

10.7.3 Alpha-pinene

Risk of formation of sensitizing peroxides on autoxidation.
Bonkovsky, et al. 1992[43] conclude that α-Pinene is porphyrogenic and poses a risk to patients with acute porphyria, all of whom have an underling defect in normal hepatic heme synthesis.

10.7.4 1,8 cineole

The CNS depression seen in animal toxicity tests sometimes does manifest in children exposed to moderate amounts of eucalyptus essential oil.(Darben et al. 1998 ; Waldman 2011 in Tisserand and Young [5])

10.7.5 Pinocamphones

The lowest known convulsant dose of Hyssop oil in human was extrapolated by Millet[42] (Centre anti-poisons Marseille, France, 1981) to be equivalent to 3 mg/Kg of isopinocamphone. That suggest a total maximal dose of 6 mg/day per adult (60 Kg)[5].

Based on the precautionary principle, the total amount of all pinocamphones should not exceed 6 mg/day per adult.

10.8 Interactions / cumulative effects with other EO or chemicals

Caution should be paid to a cumulative effect with plants and preparations containing camphor, alpha-pinene or 1,8-cineole. These 3 components are too frequent in essential oils and their chemotypes for an exhaustive list to be established.

- Camphor: *Lauraceae*, *Asteraceae*, *Lamiaceae*…
- Alpha-pinene : *Abietaceae*, *Cupressaceae*, *Lamiaceae*, *Burseraceae*, *Myrtaceae*…
- 1,8-cineole : *Myrtaceae*, *Lamiaceae*, *Lauraceae*, *Zingiberaceae*…

Certain essential oils of *Rosmarinus officinalis* L. are likely to have a cumulative effect with other plants / essential oils for the following components of health concern:

- Estragole,
- Methyleugenol,
- Pinocamphone or its isomers,
- Pulegone.

11. Permitted claims for E.O. from *Rosmarinus officinalis*

Health claims must be in accordance with the general principles of regulation 1924/2006 and the relevant regulations. You can find more information about this on the web page "Permitted claims" of the FPS Public Health.

At the time this advice was issued, there are proposals of claims, not yet approved ('on hold'), related to the use of *Rosmarinus officinalis.*

12. Recommendations for use

The presence of substances of concern for human health in the essential oil of *Rosmarinus officinalis* is generally rare, quantitatively low and may concern only certain specific chemotypes.
However, in order to prevent any risk, the use of this essential oil in food supplements should be subject to a complete analysis of each batch used with a dosage of the following active ingredients:

- 1.8 cineole,
- camphor,
- alpha-pinene,
- estragole,
- pulegone,
- methyleugenol,
- iso, α & β-pinocamphone.

For each of these components, a possible cumulative effect with the other plant extracts of the formula will be assessed.

Proposal for labeling mention:
"Do not use in case of obstruction of bile duct, cholangitis, liver disease, gallstones and any other biliary disorders that require medical supervision and advice".[40]
"Not recommended for pregnant and lactating women and for children/adolescents under 18 years old".

13. Conclusion

Considering the above information,

Considering the advices the Committee has previously issued during the sessions of 24th October 2019, 27th August 2019, 9th October 2018, 28th August 2018, 20th February 2018, 24th May 2016, 12th April 2016, 10th November 2015, 22nd September 2015, 29th January 2013 and 16th October 2012,

The Advisory Committee on Plant Preparations decides at the meeting of 22nd October 2020 the following:

The use of the E.O. of *Rosmarinus officinalis* in encapsulated dietary supplements is permitted under the following conditions:

- The E.O. of *Rosmarinus officinalis* L. must comply with the specified composition and identified chemotype as mentioned in the **Ph. Eur. (10th edition).**
- The total daily dose of **α-pinene** should not exceed 40 mg, including other sources of α-pinene present in the preparation.
- The total daily dose of **camphor** should not exceed 60 mg, including other sources of camphor present in the preparation.
- In case of presence of pulegone or isopinocamphone in the particular chemotype used:
  - the total daily dose of **pulegone** (and menthofurane) should not exceed 37,5 mg, including other sources of present in the preparation (EMA 2016[41])
  - the total daily dose of **pinocamphones** should not exceed 6 mg, including other sources of present in the preparation.
- If other sources of estragole and methyleugenol are present in the preparation, the total daily dose of the sum of **estragole + methyleugenol** should not exceed 3 mg.
- The use of this E.O. is not suitable
  - for pregnant and lactating women and children younger than 18 years
  - obstruction of bile duct, cholangitis, liver disease, gallstones and any other biliary disorders that require medical supervision and advice
- The use of this E.O. in food supplements should be limited to a maximum of 21 days
- The analysis of the essential oil used in a food supplement must determine its estragole, pulegone, methyleugenol, pinocamphones content with a minimum quantification threshold of 5.10^{-4} (0,05%).

14. References

1. Global Biodiversity Information Facility (« système mondial d'informations sur la biodiversité »)- https://www.gbif.org/species/3889108
2. International Plant Names Index - https://www.ipni.org/n/60474677-2
3. National Center for Biotehnology Information : https://www.ncbi.nlm.nih.gov/ - Toxonomy ID : 39367 - NCBI:txid39367
4. Reverchon, E., Senatore, F., 1992. Isolation of rosemary oil: comparison between hydrodistilled and supercritical fluid CO2 extraction. Flavour & Fragrance Journal 7, 227-230.
5. Tisserand R., Youg R., 2014. Essential Oil Safety – second Edition – Churchill Levingstone Elsevier, 407-409
6. Soliman, F.M., El Kashoury, E.A., Faty, M.M., et al., 1994. Analysis and biological activity of the essential oil of Rosmarinus officinalis L. from Egypt. Flavour & Fragrance Journal, 9, 29-33
7. Lawrence, B.M., 1995. Progress in essential oils. Perfumer & Flavorist 20.
8. National Library of Medecine (NCBI) - https://pubchem.ncbi.nlm.nih.gov/compound/camphor. Modify: 2020-07-04
9. Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements - European Food Safety Authority (EFSA) (2012)
10. Assessment report on Rosmarinus officinalis L. Aetheroleum EMA/HMPC/13631/2009
11. Xu H, Blair NT, Clapham DE: Camphor activates and strongly desensitizes the transient receptor potential vanilloid subtype 1 channel in a vanilloid-independent mechanism. J Neurosci. 2005 Sep 28;25(39):8924-37. doi: 10.1523/JNEUROSCI.2574-05.2005. [PubMed:16192383]
12. Gyoubu K, Miyazawa M: In vitro metabolism of (-)-camphor using human liver microsomes and CYP2A6. Biol Pharm Bull. 2007 Feb;30(2):230-3. [PubMed:17268056]
13. National Library of Medecine - PubChem CID: 444294, https://pubchem.ncbi.nlm.nih.gov/compound/L-camphor
14. The Drugbank Database, https://www.drugbank.ca/drugs/DB11345
15. CAMPHOR - National Library of Medicine HSDB Database in PubChem CID 444294
16. Metabolism-metabolites of alpha-pinene, Koppel C et al; Arch Toxicol 49 (1): 73-8 (1981) in https://pubchem.ncbi.nlm.nih.gov/compound/6654#section=Metabolism-Metabolites
17. Levin JO et al; Int Arch Occup Environ Health 63 (8): 571-3 (1992) in https://pubchem.ncbi.nlm.nih.gov/compound/6654#section=Metabolism-Metabolites
18. Falk AA et al; Scand J Work Environ Health 16 (5): 372-8 (1990) – in Pubchem ID 6654
19. Kovar et al., 1987 in EMA/HMPC/13631/2009 Assessment report on Rosmarinus officinalis L., aetheroleum and Rosmarinus officinalis L., folium – July 2010
20. ECHA – European Chemical Agency - EC / List no.: 616-767-5
21. Pubchem Monograph - https://pubchem.ncbi.nlm.nih.gov/compound/camphor
22. Takarada, K., Kimizuka, R., Takahashi, N., et al., 2004, A comparison of the antibacterial efficacies of EO against oral pathogens. Oral microbiol. Immunol. 19, 61-64
23. USEPA, https://iaspub.epa.gov/oppthpv/quicksearch.display?pChem=101069
24. European Chemical Agency - https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.006.757
25. De Vincenzi, M., Silano, M., De Vincenzi, A., et al. Constituents of aromatic plants : eucalyptol. Fitoterapia 202, 73:269-75
26. USEPA, https://iaspub.epa.gov/oppthpv/quicksearch.display?pChem=101069
27. Caldas, et al. Repeated-doses and reproductive toxicity studies of the monoterpene 1,8-cineole in Wistar rats. Food and Chemical Toxicology, Vol 97, Nov. 2016, 297-306.
28. Gomes-Carneiro M.R. et al. Mutagenicity testing of (±)camphor, 1,8-cineole, citral, citronellal, (−)-menthol and terpineol with the Salmonella/microsome assay. Mutation Research/Genetic Toxicology and Environmental Mutagenesis. Vol 416, Issues 1–2, 7 August 1998, Pages 129-136.
29. Gomes-Carneiro et al. Evaluation of β-myrcene, α-terpinene and (+)- and (−)-α-pinene in the Salmonella/microsome assay. Food and Chemical Toxicology, Volume 43, Issue 2, February 2005, Pages 247-252.
30. National Toxicology Program (NTP). 2016. NTP technical report on the toxicity studies of α-pinene (CASRN 80-56-8) administered by inhalation to F344/N rats and B6C3F1/N mice. Research Triangle Park, NC: National Toxicology Program. Toxicity Report 81.

31. Wei,F.X., Liu, J.X., Wang, L., et al., 2008. Expression of bcl-2 and bax genes in the liver cancer cell line HepG2 after apoptosis induced by essential oils from Rosmarinus officinalis. Zhong Yao Cai 31, 877-879
32. Sasaki Y-F. et al. Modifying effects of components of plant essence on the induction of sister chromatid exchanges in cultured Chinese hamster ovary cells. Mutation Research, 226 (1989) 103-110.
33. Vuković-Gačić B . et al. Antimutagenic effect of essential oil of sage (Salvia officinalis L.) and its monoterpenes against UV-induced mutations in Escherichia coli and Saccharomyces cerevisiae. Food and Chemical Toxicology. Volume 44, Issue 10, October 2006, Pages 1730-1738.
34. Hayes, A.J., Leach, D.N., Markham, J.L., 1997. In vitro cytotoxicity of Australian Tea-tree oil using human cell lines. Journal of essential oil Research 9, 575-582.
35. National Toxicology Program, Institute of Environmental Health Sciences, National Institutes of Health (NTP). 1992. National Toxicology Program Chemical Repository Database. Research Triangle Park, North Carolina.
36. Bonkovsky, H.L., Cable, E.E., Cable, J.W.,et al. 1992. Porphyrogenic properties of the terpenes camphor, pinene, and thuyone. Biochem. Pharmacol. 43, 2359-2368.
37. Dr Jean Valnet, Aromathérapie : Traitement des maladies par les essences des plantes, Editions Maloine, janvier 1966.
38. Kew Science, https://wcsp.science.kew.org/nonacceptedRef.do?name_id=179873,
39. Al-Heder, A., Hasam Z.A., Aqel, M.B., 1994 Hyperglycemic and insulin release inhibitory effects of Rosmarinus officinalis, J. Ethnopharmacolgy 43, 217-221
40. Community herbal monograph on Rosmarinus officinalis L., aetheroleum - EMA/HMPC/235453/2009
41. Public statement on the use of herbal medicinal products containing pulegone and menthofuran. EMA2016 https://www.ema.europa.eu/en/documents/scientific-guideline/public-statement-use-herbal-medicinal-products1-containing-pulegone-menthofuran-revision-1_en.pdf
42. Y. Millet, J. Jouglard, M. D. Steinmetz, P. Tognetti, P. Joanny & J. Arditti (1981) Toxicity of Some Essential Plant Oils. Clinical and Experimental Study, Clinical Toxicology, 18:12, 1485-1498, DOI: 10.3109/15563658108990357
43. Bonkovsky, Herbert & Cable, Ed & Cable, Julia & Donohue, Susan & White, Emily & Greene, Yvonne & Lambrecht, Richard & Srivastava, Kishore & Arnold, Wilfred. (1992). Porphyrogenic properties of the terpenes camphor, pinene, and thujone (with a note on historic implications for absinthe and the illness of Vincent van Gogh). Biochemical pharmacology. 43. 2359-68. 10.1016/0006-2952(92)90314-9.
44. INCHEM - http://www.inchem.org/documents/ukpids/ukpids/ukpid19.htm
45. American Conference of Governmental Industrial Hygienists. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH 2014, p. 17