



16 September 2010  
EMA/638578/2009  
Committee on Herbal Medicinal Products (HMPC)

**This document was valid from 16 September 2010 until 8 July 2020.**

## Overview of comments received on Community herbal monograph on *Thymus vulgaris* L., *Thymus zygis* Loefl. ex L., aetheroleum (EMA/HMPC/131901/2009)

Table 1: Organisations and/or individuals that commented on the draft Community list entry on *Thymus vulgaris* L., *Thymus zygis* Loefl. ex L., aetheroleum as released for public consultation on 15 June 2009 until 15 September 2009.

	Organisations and/or individuals
1	AESGP



Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	Comment and Rationale	Outcome
AESGP	AESGP welcomes the draft Community Monograph on <i>Thymus vulgaris</i> and <i>Thymus zygis</i> aetheroleum	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	Interested party	Comment and Rationale	Outcome
4.2 Posology and method of administration	AESGP	<p><b>Comments:</b></p> <p><u>Cutaneous use:</u> The limitation of the use in children and adolescent under 18 years of age seems exaggerated with regards to the data available on the cutaneous use.</p> <p>Thyme oil bathes, e.g. the Thymian Li-iL Erkältungs-Bad (Germany) are traditionally used also in children. The use of thyme oil in bathes for children has been examined in an observational study (1972-1973) which involved 84 children between 1 and 14 years of age suffering from acute or chronic sinusitis. The tolerability was estimated as good by the authors who therefore expressively supported the therapeutic use of thyme oil bathes for the treatment of sinusitis in children [Busch-Petersen &amp; Hein 1975].</p> <p>E.g. Thymian Li-iL Erkältungs-Bad (5g thyme oil/ 100g) has a</p>	<p>Age limit:</p> <p>For the cutaneous use no safety data from the paediatric population are available. Additionally no data on the posology are published for children and adolescents. Therefore the oral and cutaneous uses should be limited to adults and elderly.</p> <p>Bath additive: age limit of 3 years acceptable, because authorised products are used in this age group without reports of any concerns.</p>

SPECIFIC COMMENTS ON TEXT

	<p>long tradition of use in children. The German review process resulted in a restriction of age from 2 years on. To the company's best knowledge there is no data available on potential adverse effects in children, pregnant and breastfeeding women. A worldwide literature search did not result in any indications that would lead to exclusion of children under 6 years of age.</p> <p>Furthermore, thyme oil is widely used in cosmetics. The German BfR (Bundesinstitut für Risikobewertung, Federal Institute for Risk Assessment) has published a statement on the use of essential oils in cosmetics on 28 February 2008 (FAQ: Questions and Answers on the use of essential oils) stating that a use of thyme oil in children under 3 years of age may cause problems. Unlike other substances the Institute does not recommend a concentration of use for thyme oil.</p> <p>Indeed the reference "Plants in cosmetics – volume III – potentially harmful components" section "thymol" and a joined FAO/WHO expert committee on food additives concluded that there is no safety concern related to thymol. The final recommendation of the Committee of experts on cosmetic products is that thymol should not be used in cosmetic products for children below the age of 3 years. Though thymol is not the only constituent of the thyme essential oil (it accounts for 0 to 60% of the essential oil), it is the main component and the one with the highest toxicity.</p> <p><b>Proposed change (if any):</b> indication 2)</p>	<p>Liquid dosage forms: endorsed</p>
--	---	--------------------------------------

SPECIFIC COMMENTS ON TEXT		
		<p>Cutaneous use:</p> <p>The use in children under 3 years is not recommended.</p> <p>Use as bath additive:</p> <p>The use in children under 3 years of age is not recommended because medical advice should be sought.</p> <p><u>Liquid dosage form</u></p> <p>The dosage form "liquid dosage form for cutaneous use" has not been included in section 4.2 (posology and method of administration) although it is mentioned under section 3 (pharmaceutical form) as suitable for indication 2: "liquid or semi-solid dosage forms for oral (indication 1) and cutaneous use and as a bath additive (indication 2)".</p> <p>The liquid dosage form should therefore be included in section 4.2, under the same conditions as the semi-solid dosage form, both being intended for cutaneous use. In accordance with this we suggest the following wording:</p> <p><b>Indication 2)</b></p> <p><i>Adults and elderly</i></p> <p>Cutaneous use: in <u>liquid or semi-solid</u> dosage forms in concentrations up to 10%; apply up to 3 times daily".</p>
Other comments	AESGP	<p>The HMPC meeting report of 13-14 May 2009 reported that the <b>"Committee could not adopt a draft list entry on <i>Thymus vulgaris</i> L.; <i>Thymus zygis</i> L., aetheroleum for release for public consultation because of insufficient supporting genotoxicity data according to the guideline on the assessment of genotoxicity of herbal substances/preparations (EMA/HMPC/107079/07)".</b></p> <p>Potential mutagenicity and genotoxicity of thyme essential oil and its main components, especially thymol, has been assessed in a number of studies on both prokaryotic and eukaryotic in vitro and in vivo experimental systems. Studies have many weaknesses, findings are often contradictory and reporting does not always contain sufficient details, which make</p>

SPECIFIC COMMENTS ON TEXT

	<p><i>The genotoxicity guideline states that "if the tests were considered to have been performed according to the ICH guidelines and the result is <b>unequivocally negative, no further genotoxicity testing is required on the basis of HMPC non-clinical guideline. A negative test result fulfils the genotoxicity testing requirements for including a herbal substance or preparation in the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products</b>".</i></p> <p>On this matter, section 5.3 Preclinical safety data reads that <b>"Thyme essential oil had no mutagenic or DNA-damaging activity in either the AMES test (strains TA1535, TA1537, TA98, TA100, with and without metabolic activation) or Bacillus subtilis rec-assay."</b> The strains of Salmonella typhimurium are those advised in the OECD guidelines. Although Bacillus subtilis "rec-assay" is not mentioned in the OECD nor the ICH guideline, it is a widely used test for the detection of DNA-damaging agents and its extreme sensitivity makes it a test of reference for the detection of genotoxic agents in the environment. Mazza states that <i>"the rec-assay is one of the simplest and fastest microbial assays and in combination with other microbial systems, has allowed several authors to detect a number of new mutagens.[...] compared with other microbial repair tests E.coli or salmonella, the rec assay offers several advantages [...] [its] applicability does not suffer from the limitation imposed on other microbial assays by strong bactericidal compounds and may provide good evidence of DNA interaction and damage."</i></p> <p>The WHO monograph on Herba Thymi states that <i>"Thyme</i></p>	<p>interpretation difficult and conclusions equivocal. Thymol is also an antioxidant and prevents DNA damage in certain experimental conditions. It seems that in some studies thyme oil and its main components give weak indications towards genotoxicity, but at the best these indications are weak and debatable. Adequately performed mammalian cell studies are needed for the resolution of potential genotoxicity. However, the data are sufficient to demonstrate safety for the cutaneous application. Therefore a list entry is proposed for the cutaneous use only.</p>
--	---	--

SPECIFIC COMMENTS ON TEXT

*essential oil did not have any mutagenic activity in Bacillus subtilis rec-assay or the Salmonella/microsome reversion assay. Recent investigations suggest that thyme extracts are antimutagenic and that luteolin, a constituent of thyme, is a strong antimutagen against the dietary carcinogen Trp-P-2."*

**Based on the above rational, we seriously question the Committee's decision not to adopt the draft list entry due to insufficient genotoxicity data and we formally ask the Committee to reconsider its decision. We would also find useful to have the detailed rational leading to this decision.**

**References:**

Plants used in cosmetics - Volume III: Potentially harmful components (2006). Council of Europe Publishing.

Busch-Petersen D, Hein J. Zur Therapie der paranasalen Sinusitiden im Kindesalter mit Li-iL-Thymian-Bädern. medicamentum 1975; 16:51-53.

WHO monograph 'Herba Thymi'

<http://etnof.fciencias.unam.mx/P4Mat/M6-Thymi.pdf>

Mazza G. *Bacillus subtilis* "rec Assay" Test with Isogenic Strains. Applied and Environmental Microbiology 1982; 43: 177-184