



London, 23 November 2005  
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**OVERVIEW OF COMMENTS RECEIVED ON  
'PUBLIC STATEMENT ON THE USE OF HERBAL MEDICINAL  
PRODUCTS CONTAINING ESTRAGOLE'  
AND ON  
'PUBLIC STATEMENT ON THE USE OF HERBAL MEDICINAL  
PRODUCTS CONTAINING METHYLEUGENOL'**

*Table 1: Organisations that commented on the document as released for consultation*

	Organisation
1.	Association of the European Self-Medication Industry (AESGP)

Table 2: Discussion of comments

Line no or section and paragraph no	Comment and rationale	Outcome / Proposed change
<p>Conclusions and recommendations</p>	<p>Following previous comments (submitted on 28 October 2003), the sentence “<i>exposure of ME/ ES to sensitive groups such as children, pregnant and breast-feeding women should be avoided</i>” was changed to “... <i>should be minimised</i>”. This modification is welcome.</p> <p>However, organisation commenting still believes that on basis of the following comments the sentence “<i>exposure of ME/ ES to sensitive groups such as children, pregnant and breast-feeding women should be minimised</i>” should be deleted in both drafts.</p> <p>The rationale for this recommendation is the following:</p> <p>A number of plants containing Estragole and Methyleugenol are almost exclusively used in food. As a consequence, human exposure to these substances mainly results from the consumption of food products, for example: anise, fennel, basil, tarragon, Jamaica pepper, cardamom or cloves.</p>	<p>The HMPC reviewed the comments received and decided to maintain its recommendation with slight modification regarding the minimum exposure of sensitive groups to ME/ES for the following reasons:</p> <ol style="list-style-type: none"> <li>1. In contrast to the food products area, herbal medicinal products are assessed from a safety point of view in a regulatory framework. Applicants wishing to market ME/ES containing herbal medicinal products have the opportunity to reduce the ME/ES content in these products.</li> <li>2. The consumption of ME/ES containing herbal medicinal products represents an additional ME/ES exposure to the exposure resulting from food intake. The HMPC considers that this is particularly relevant for <i>young</i> children, pregnant and breast-feeding women.</li> </ol>

	<p>Data show that Estragole and Methyleugenol, like some other phenylpropanoids with allyl-function (e.g. safrole or <math>\beta</math>-asarone), may be carcinogenic when administered as pure substances at high doses in rodents. The minimal carcinogenic dose of Estragole and Methyleugenol in animals is between <math>1 \times 10^{20} - 1 \times 10^{21}</math> molecules/kg bm. This is 1.000 - 10.000 times higher than the intake of regular pesto-eaters! The population with the presumably highest dietary consumption of Estragole and Methyleugenol ingests negligible quantities reaching ca <math>10^{16} - 10^{17}</math> molecules/kg bm <sup>1</sup>.</p> <p>It must be emphasised that a systematic reassessment of rodent carcinogenicity of Methyleugenol and Estragole recently published by WADDELL <sup>2 3</sup> clearly questioned earlier assumptions. Waddell emphasises that carcinogenicity studies are normally performed with inbred animals with very low genetic variability while humans express a much wider range of genetic metabolism variability. The author shows that the data available tend to invalidate (rather than support) the probability of a carcinogenic risk of Methyleugenol and Estragole at current level of human exposure.</p>	

<sup>1</sup> Waddell W.J. et al., Thresholds of Carcinogenicity of Flavors, Toxicological sciences 68, 2002, S. 275 - 279

<sup>2</sup> Waddell, W.J., Thresholds in Chemical Carcinogenesis: What Are Animal Experiments Telling Us?, Toxicologic Pathology, 2003, S. 260 - 262

<sup>3</sup> Waddell W.J., Threshold for carcinogenicity of N-nitrosodiethylamine for esophageal tumors in rats, Food and Chemical Toxicology 41, 2003, S. 739 - 741