ESTRAGOLE

CAS N°: 140-67-0 **Empirical formula:** $C_{10}H_{12}O$

Synonyms: *p*-Allylanisole
1-Allyl-4-methoxybenzene
Benzene, 1-methoxy-4-(2-propenyl)-
Chavicyl methyl ether
Isoanethole
p-Methoxyallylbenzene
1-Methoxy-4-(2-propen-1-yl)benzene
Methyl chavicol

History: Initial reviews: New Standard

Current revision date: 2009

Implementation date: for new submissions*: August 7, 2009

for existing fragrance compounds*: August 7, 2010

Next review date: 2014

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

Standard: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin-contact products:

Leave-on products: see note box

Rinse-off products: see note box
including household cleaning products

Non skin-contact products: see note box

Note box: The total concentration of Estragole should not exceed the following limitations in the finished product:
Fine fragrance and Eau de Toilette: 0.2%
Other leave on and rinse-off cosmetic products: 0.01%
Non skin and non cosmetic products: 0.2%

Fragrance material specification: N/A

Contribution from other sources: See **Annex I**

Critical effect: **Carcinogenicity**

E S T R A G O L E

REXPAN Rationale / Conclusion:

Although Estragole has been shown to cause tumors in laboratory animals (NTP, 2008) the studies have a number of limitations that have an impact on its direct application to human risk and particularly risk from dermal contact:

1. The current studies are confounded by high dose toxicity including significant hepatotoxicity, gastric damage and malnutrition in both mice and rats. This makes the distinction between primary and secondary mechanisms of tumour formation difficult.

2. Current scientific evidence supports a non-linear relationship between dose and the potential for carcinogenicity of Estragole and related substances (Smith et al., 2002). This is due to differences in the way that Estragole is metabolized at high versus low doses. Studies indicate that all these events are likely to be minimal in the dose range of 1- 10 mg/kg body weight (Zangouras et al., 1981; Anthony et al., 1987). The lowest dose in the NTP 90-day study used in this assessment was 37.5 mg/kg bw/d thus care needs to be taken in extrapolating to lower doses relevant to fragrance exposure. This non-linear response has also been used to support the risk assessment for exposure to Estragole in Flavours.

Consideration also needs to given to differences between dermal and oral exposure. Introduction of a bolus dose of test material into the stomach leads to higher peak blood plasma levels and increased metabolic demand compared with the slower, more steady absorption of the substance from the skin. Furthermore, although no data exist on the skin metabolism of Estragole or related compounds there is evidence that many enzymatic processes, particularly oxidative ones, are much lower in the skin than in the liver (Bronaugh et al., 1995). Thus the relevance of reported tumours resulting from skin painting studies or subcutaneous injection (Miller et al., 1983) with putative genotoxic metabolites of Estragole needs to be put into perspective. Although data indicate that the most potent metabolite for inducing skin tumours in rodents is the1′-hydroxy epoxide metabolite, characterization of dermal metabolism has not been established to show that the epoxide metabolites used in the skin painting and subcutaneous injection studies would be the metabolite of concern in either rat or mouse, nor has it been established that the level of exposure is relevant as it is unlikely that significant local tissue concentrations for metabolites would result from a realistic oral ingestion or dermal application of Estragole.

The total dermal exposure resulting from the limited use of Estragole as described in this Standard is 0.04 mg/kg body weight/day. Making the following conservative assumptions:

- 100% dermal absorption
- Metabolism human = rodent
- Metabolism skin = liver
- Oral LOEL = 37.5 mg/kg/day – based on rat oral low dose observed hyperplasia (oval, bile cell) and it assumes that the hyperplasia will progress to tumor formation
- UF = 1,000 (10 for LOEL to NOAEL, 10 for species, 10 for inter-individual variability)

Worst Case Risk Assessment

- Systemic RfD = 37.5/1,000 = 0.04 mg/kg/day

The IFRA Standard reflects the potential for the higher presence of Estragole in hydroalcoholic and air freshener products whilst ensuring that the RfD for cumulative exposure through all product types will not be exceeded.

E S T R A G O L E

References:

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Smith R.L., Adams T.B., Doullc J., Ferond V.J., Goodmane J.I., Marnettf L.J., Portogheseg P.S., Waddellh W.J., Wagneri B.M., Rogers A.E., Caldwellk J., and Sipes I.G. 2002. Safety assessment of allylalkoxybenzene derivatives used as flavoring substances — methyl eugenol and estragole. Food and Chemical Toxicology 40: 851–870

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