Isoeugenol

CAS N°: 97-54-1 **Empirical formula:** $C_{10}H_{12}O_2$

Synonyms: 1-Hydroxy-2-methoxy-4-propen-1-ylbenzene
4-Hydroxy-3-methoxy-1-propen-1-ylbenzene
4-Hydroxy-3-methoxy-1-propenylbenzene
iso-Eugenol
3-Methoxy-4-hydroxy-1-propen-1-ylbenzene
2-Methoxy-4-propenylphenol
2-Methoxy-4-(1-propenyl)phenol
Phenol, 2-methoxy-4-(1-propenyl)-
4-Propenylguaiacol

History:

Initial reviews:	May 1980 (6th Amendment), May 1998 (31st amendment), 2001, April 2004 (38th Amendment), May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date:	2013	

* 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:
For a description of the categories, refer to the QRA Informational Booklet.

Category 1: See Note box (1)	0.01 %	Category 7:	0.02 %
Category 2:	0.01 %	Category 8:	0.02 %
Category 3:	0.02 %	Category 9:	0.02 %
Category 4:	0.02 %	Category 10:	0.02 %
Category 5:	0.02 %	Category 11: Not Restricted (2)	
Category 6: See Note box (1)	0.2 %		

Note box:
For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Isoeugenol

Fragrance material specification: N/A

Contribution from other sources: See Annex 1

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean **EC_3** values ($\mu g/cm^2$) [No. Studies]	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL[3]** ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	**NOEL – HMT** (induction) ($\mu g/cm^2$)	**LOEL[2]** (induction) ($\mu g/cm^2$)	
498 [18]	Moderate	250[4]	NA	775	250

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;

LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003

[2] Data derived from HRIPT or HMT

[3] WoE NESIL limited to three significant figures

[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Isoeugenol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 250 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Isoeugenol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Basketter, D. A., Lea, L. J., Dickens, A., Briggs, D., Pate, I., Dearman, R. J.,Kimber, I., 1999. A comparison of statistical approaches to the derivation of EC3 values from local lymph node assay dose responses. *Journal of Applied Toxicology*, 19(4), 261-266.

Basketter, D. A., Wright, Z., Gilmour, N. J., Ryan, C. A., Gerberick, G. F., Robinson, M. K., Dearman, R. J.,Kimber, I., 2002. Prediction of human sensitization potency using local lymph node assay EC3 values. *The Toxicologist*, 66(1-S), 240

Loveless, S. E., Ladics, G. S., Gerberick, G. F., Ryan, C. A., Basketter, D. A., Scholes, E. W., House, R. V., Hilton, J., Dearman, R. J.,Kimber, I., 1996. Further evaluation of the local lymph node assay in the final phase of an international collaborative trial. *Toxicology*, 108 (1-2), 141-152

RIFM (Research Institute for Fragrance Materials, Inc.), 1991. Murine local lymph node assay on isoeugenol. Unpublished report from Firmenich Incorporated, 24 August. Report number 40676 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Murine local lymph node assay with methoxy dicyclopentadiene carboxaldehyde. Unpublished report from Firmenich

Isoeugenol

Incorporated, 08 October. Report number 42120 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001a. Murine local lymph node assay with 3-cyclopentene-1-butanal, alpha,2,2,3-tetramethyl-.gamma.-methylene. Unpublished report from Firmenich Incorporated, 30 November. Report number 42122 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001b. 4-Penten-2-ol, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-: Murine local lymph node assay. Unpublished report from Firmenich Incorporated, 11 November. Report Number 42130 (RIFM, Woodcliff Lake, NJ, USA)

RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Murine local lymph node assay with methyl hexadecanoate. Unpublished report from Firmenich Incorporated, 22 January. Report number 42123 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2002a. Murine local lymph node assay of delta-1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-2-buten-1-one. Unpublished report from Firmenich Incorporated, 02 April. Report number 42139 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2002b. 2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4,4a-dimethyl-6-(1-methylethylidene)-, (4R,4aS)-: Murine Local Lymph Node Assay. Unpublished report from Firmenich Incorporated, 31 January. Report number 42145 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2002c. Methyl octanoate: Murine lymph node assay. Unpublished report from Firmenich Incorporated, 12 September. Report number 42131 (RIFM, Woodcliff Lake, NJ, USA). Thompson, G. R., Booman, K. A., Dorsky, J., Kohrman, K. A., Rothenstein, A. S., Schwoeppe, E. A., Sedlak, R. I.,Steltenkamp, R. J., 1983. Isoeugenol: A survey of consumer patch-test sensitization. Food and Chemical Toxicology, 21(6), 735-740.

Wright, Z. M., Basketter, D. A., Blaikie, L., Cooper, K. J., Warbrick, E. V., Dearman, R. J.,Kimber, I., 2001. Vehicle effects on skin sensitization potency of four chemicals assessment using the local lymph node assay. *International Journal of Cosmetic Science*, 23(2), 75-83.