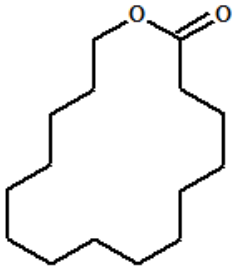
Cyclopentadecanolide

CAS N°:	106-02-5	**Empirical formula:**	$C_{15}H_{28}O_2$
		Structure:	
Synonyms:	Angelica lactone Cyclopentadecanolide 15-Hydroxypentadecanoic acid, ω-lactone Oxacyclohexadecan-2-one Pentadecalactone ω-Pentadecalactone Pentadecanolide Cyclopentadecanolid Supra (commercial name) Exaltex (commercial name) Exaltolide (commercial name) Macrolide (commercial name) Muskalactone (commercial name) Pentalide (commercial name) Thibetolide (commercial name)		

History:	Initial reviews:	New Standard	
	Current revision date:	June 2013	
	Implementation date:	For new submissions*:	August 10, 2013
		For existing fragrance compounds*:	August 10, 2014
	Next review date	2018	

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

RECOMMENDATION:	**RESTRICTED**

RESTRICTIONS:

Limits in the finished product:			
Category 1 See Note box (1)	0.16 %	Category 7	0.42 %
Category 2	0.20 %	Category 8	2.00 %
Category 3	0.83 %	Category 9	5.00 %
Category 4	2.50 %	Category 10	2.50 %
Category 5	1.31 %	Category 11	See Note box (2)
Category 6	3.93 %		

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Note box:
(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 - www.iofiorg.org) (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.

Fragrance material specifications:	N/A

CONTRIBUTION FROM OTHER SOURCES:

See **Annex I**

CRITICAL EFFECT:	SENSITIZATION

RIFM SUMMARIES:

LLNA weighted mean EC3 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) ($\mu g/cm^2$)	
>12,500 [1][4]	Weak	5500[5]	6900[5]	NA	5500

All data in this table are available from RIFM and are listed in the RIFM Database.
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 two significant figures.
[4]EC3 value from one LLNA conducted on a high purity material, not the mean. LLNA data from three commercial samples, with varying degrees of impurities, resulted in a range of EC3 values (<2500 – 6375 $\mu g/cm^2$).
[5]HRIPT and HMT conducted on commercial materials.

REXPAN RATIONALE / CONCLUSION:

The RIFM Expert Panel reviewed the critical effect data for Cyclopentadecanolide and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 5500 $\mu g/cm^2$. The material may contain unidentified impurities that have potential to induce sensitization. While a purified material shows no potential for dermal sensitization in an LLNA, the impurities remain unidentified. As such the NESIL is based on the commercial material. The Panel recommends the limits for the 11 different product categories, which are the acceptable use levels of Cyclopentadecanolide 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 publication by Api *et al*., 2008.

REFERENCES:

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick GF, et al. Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients. *Regulatory Toxicology and Pharmacology* 2008;52(1): 3-23.

RIFM (Research Institute for Fragrance Materials, Inc.), 1974. Report on human maximization studies. RIFM report number 1779 06/05A. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Repeated insult patch test with ω--pentadecalactone. Unpublished study from Symrise GmbH & Co. KG, 21 October. Report number 60740. (RIFM, Woodcliff Lake, NJ, USA).

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RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Local Lymph Node Assay. Unpublished study from Symrise GmbH & Co. KG, 21 October. Report number 60740. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Local Lymph Node Assay. Unpublished study from Symrise GmbH & Co. KG, 21 October. Report number 60741. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Local Lymph Node Assay. Unpublished study from Symrise GmbH & Co. KG, 2 December. Report number 60742. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Local Lymph Node Assay. Unpublished study from Symrise GmbH & Co. KG, 21 January. Report number 60743. (RIFM, Woodcliff Lake, NJ, USA).