Substance Information Document

L-Menthol

1. Substance identity

Name	L-Menthol
Synonyms	(1R,3R,4S)-5-Methyl-2-(1-methylethyl)-cyclohexanol; (-)-Menthol
IUPAC Name	(1R,2S,5R)-5-methyl-2-propan-2-ylcyclohexan-1-ol
CAS	2216-51-5 (information on CAS 89-78-1 also included)

2. Toxicological information

Menthol" was considered by EFSA and JECFA expert groups to show no genotoxic potential. No evidence of mutagenic potential was seen in several bacterial reverse mutation (Ames) tests with DL-menthol and L-menthol. No carcinogenicity was seen in rats or mice after DL-menthol dietary administration, providing about 375 and 600 mg/kg bw/day, respectively, for 2 years. An extended one-generation reproductive toxicity (EOGRT) revealed NOELs to be 419-499 mg/kg bw/day for male rats and 455-594 mg/kg bw/day for female rats, based on lower litter sizes in the high-dose groups in both generations (DL-menthol dietary administration).
Menthol is irritating to the skin, eyes and respiratory tract. Local effects on the oral and gastrointestinal mucosa have also been reported. It is a skin sensitiser in a small proportion of exposed individuals, although not in laboratory animal tests, respiratory tract sensitization was assumed in a few case studies.
It is not acutely toxic by inhalation, with a 4-hour LC_{50} value in rats of 5289 mg/m^3(nose-only exposure of DL-menthol). Reported oral LD_{50} values were 2652-4384mg/kg bw in mice and 940-3180mg/kg bw in rats, indicating a moderate-low order of acute oral toxicity.
Repeated inhalation exposure to L-menthol at 1.66 mg/m^3 for 10 weeks in rats, but not at 0.95 mg/m^3, induced lung congestion and inflammation. Liver and kidney toxicity (including fatty degeneration and necrotic foci) were reported in mice after exposure to menthol at 50 or 100mg/m3for 5hours/day for 84days.
Oral NOAELs of 375 and 600 mg/kg bw/day were established for rats and mice, respectively, in chronic dietary studies. The REACH registrants for DL-menthol have adopted the lowest dose in the rat study (188mg/kg bw/day) as the point of departure for the calculation of an inhalation DNEL, while the registrants for L-menthol used the NOAEL of 375 mg/kg bw/day.
JECFA has derived an oral ADI of 4 mg/kg bw for DL-menthol.

JECFA	930. Menthol (WHO Food Additives Series 42) (inchem.org) Safety evaluation of certain food additives: prepared by the eighty-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) WHO_TRS_891.pdf;jsessionid=330742720C666FC28D0817EB786CEBA7

FEMA	3. GRAS Substances(2001-3124)_0.pdf (femaflavor.org)
EFSA	Scientific Opinion on Flavouring Group Evaluation 9, Revision 6 (FGE.09Rev6): Secondary alicyclic saturated and unsaturated alcohols, ketones and esters containing secondary alicyclic alcohols from chemical group 8 and 30, and an ester of a phenol derivative from chemical group 25 (wiley.com) Scientific Opinion on Flavouring Group Evaluation 90, Revision 1 (FGE.90Rev1): consideration of six substances evaluated by JECFA (68th meeting) structurally related to aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters evaluated by EFSA in FGE.18Rev1 and FGE.75Rev1 (wiley.com) Flavouring Group Evaluation 51, Revision 2 (FGE.51Rev2): Consideration of alicyclic ketones and secondary alcohols and related esters evaluated by JECFA (59th meeting) structurally related to alicyclic ketones secondary alcohols and related esters in FGE.09Rev6 (2015) (wiley.com)
ECHA – REACH dossier	Registration Dossier - ECHA (europa.eu)
PUBCHEM	l-Menthol | C10H20O - PubChem (nih.gov)
CIR	-
OSHA	-

3. Addictiveness and attractiveness

The German Cancer Research Centre report on Additives in Tobacco Products indicates an effect on the CNS ("brain stimulant or depressant") and that menthol can increase nerve activity which "consequently enhances tobacco reinforcement and addiction and provides a substitute for nicotine". In a recent survey of 1726 young adults (aged 18-24) who had smoked in the past year, menthol was rated as more appealing than non-menthol smoking, and appeal indices were linked to increased smoking intensity and reduced harm perceptions.

Both the European Commission's Scientific Committee on Health, Environmental and Emerging Risks and their Scientific Committee on Emerging and Newly Identified Health Risks report that menthol is a local anaesthetic (and cooling agent), analgesic and antitussive agent, and that it has been shown to enhance nicotine bioavailability and to facilitate nicotine self-administration. The English abstract of a Spanish report provides brief details on a case in which a 53-year-old woman exhibited craving and an excessive consumption of menthol sweets (100/day).

In summary, with respect to abuse liability, menthol acts as a local anaesthetic, supresses coughing and pain, and reduces irritation caused by nicotine, and as such, it may facilitate addictiveness.

SCENIHR	Final Opinion on Additives used in tobacco products (Opinion 1) (europa.eu)

EMA	-
PUBMED	PITOC_Additives_in_Tobacco_Products_Report.pdf (dkfz.de) Affirming the Abuse Liability and Addiction Potential of Menthol: Differences in Subjective Appeal to Smoking Menthol Versus Non-Menthol Cigarettes Across African American and White Young Adult Smokers - PubMed (nih.gov) (Online ahead of print;from abstract only) Additives used in tobacco products (europa.eu) Menthol facilitates the intravenous self-administration of nicotine in rats - PubMed (nih.gov)