

## Substance Information Document

## Menthone

## 1. Substance identity

Name	Menthone
Synonyms	<i>trans</i> -Menthone; <i>trans</i> -5-Methyl-2-(1-methylethyl) cyclohexanone; 2-Isopropyl-5-methyl-cyclohexanone; <i>para</i> -Menthane-3-one; D,L-Menthone; (±)-Menthone; Menthone racemic; <i>trans</i> -Menthane-3-one
IUPAC Name	(2S,5R)-5-methyl-2-propan-2-ylcyclohexan-1-one
CAS	14073-97-3

## 2. Toxicological information

No respiratory, oral, and eye irritation/sensitization human data are available. Eye irritation in rabbit was assessed, showing mild or no irritation. In regards to skin irritation/sensitization, an 8%-25% menthone patch solution did not cause irritation in humans, while it was observed in a 24 h-exposure study in rats. In silico modelling predicted lack of severe dermal irritation (Danish (Q)SAR database).

Acute toxicity inhalation, dermal, and oral data are not available for humans, while in rats the LD<sub>50</sub> values of 500 to 2119 mg/kg bw have been reported for oral administration of menthone from various studies, indicating a moderate acute toxicity. A very low acute dermal toxicity was shown (LD<sub>50</sub> value 4500-5000 mg/Kg bw).

In relation to repeated-dose toxicity, no overt signs of toxicity were reported in 24 patients taking a gallstone including 6% menthone (36 mg/day). In rats taking menthone orally, NOAEL was 400 mg/kg bw/day. No inhaled repeated-dose toxicity data in human were identified.

EFSA and FEMA indicated that according to the available data, menthone did not exhibit genotoxic potential. Additionally, (Q)SAR in silico investigations predicted non-genotoxicity.

No data are available for menthone for carcinogenicity. However, NICNAS inferred from the menthol data that menthone is not expected to be carcinogenic.

NICNAS noted that, although no specific reproductive studies have been undertaken with menthone or the closely related chemical menthol, the long history of human exposure to the chemicals in food have not indicated any reproductive or developmental toxicity. Animal studies confirmed this statement. No cardiopulmonary effects were observed in rats exposed to 800 mg/kg bw/day menthone by oral gavage for 28 days.

JECFA and EFSA concluded that the use of menthone as food flavoring is of "no safety concern" at then-current estimated intakes in Europe and the US.

JECFA	<a href="#">947. Substances structurally related to menthol (WHO Food Additives Series 42) (inchem.org)</a>
FEMA	<a href="#">MENTHONE   FEMA (femaflavor.org)</a>

EFSA	<a href="#">Safety and efficacy of secondary alicyclic saturated and unsaturated alcohols, ketones, ketals and esters with ketals containing alicyclic alcohols or ketones and esters containing secondary alicyclic alcohols from chemical group 8 when used as flavourings for all animal species (wiley.com)</a>  <a href="#">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)</a>
ECHA – REACH dossier	<a href="#">Registration Dossier - ECHA (europa.eu)</a>
PUBCHEM	<a href="#">Menthone   C10H18O - PubChem (nih.gov)</a>
CIR	-
OSHA	-

### 3. Addictiveness and attractiveness

Animal studies points to a reduction of the sleep time in mice with a 500 mg/kg bw dose of menthone. No sedative effects were noted (100-800 mg/Kg bw). Antidepressant effects were shown in mice subjected to unpredictable chronic mild stress. In vitro studies showed that highly potent inhibition of P450 2A6 in liver microsome was not observed by menthol analogues. Another in vitro study suggested possible local anaesthetic activity due to a suppressive effect on frog sciatic nerves.

Menthone was found in 3% of the e-liquids in the Dutch market. The investigators noted that such flavorings increase e-cigarette attractiveness and use and thereby exposure to potentially toxic ingredients.

SCENIHR	-
EMA	-
PUBMED	<a href="#">Comprehensive overview of common e-liquid ingredients and how they can be used to predict an e-liquid's flavour category</a>  <a href="#">Central stimulating properties of some terpenes</a>  <a href="#">Inhibition by menthol and its related chemicals of compound action potentials in frog sciatic nerves</a>  <a href="#">Ambulation-promoting effect of peppermint oil and identification of its active constituents</a>  <a href="#">L-menthone confers antidepressant-like effects in an unpredictable chronic mild stress mouse model via NLRP3 inflammasome-mediated inflammatory cytokines and central neurotransmitters</a>  <a href="#">Inhibition of human liver microsomal (S)-nicotine oxidation by (-)-menthol and analogues</a>



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