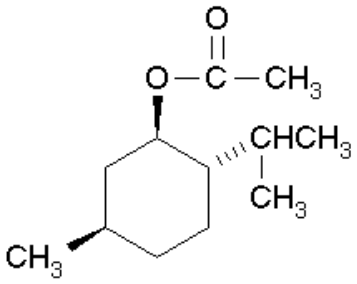
MENTHYL ACETATE, L

SYNONYMS

Cyclohexanol, 5-methyl-2-(1-methylethyl)-, acetate, [1R-(1.alpha.,2.beta.,5.alpha.)]- (9CI)
Menthol, acetate, (1R,3R,4S)-(-)- (8CI)
Acetic acid, p-menth-3-yl ester, L-
Cyclohexan-1-ol, 2-isopropyl-5-methyl-, acetate, L-
L-Menthyl acetate
L-p-Menth-3-yl acetate
(-)-Menthyl acetate

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_{12}H_{22}O_2$

IDENTIFIER DETAILS

CAS Number	:	2623-23-6, 16409-45-3 (Menthyl acetate), 29066-34-0 (dl-Menthyl acetate)
CoE Number	:	206
FEMA	:	2668
EINECS Number	:	240-459-6
E Number	:	-

CLP CLASSIFICATION

Ingredient CLP Classification: No

Endpoint	Classification	Category
Acute Oral Toxicity	-	-
Acute Dermal Toxicity	-	-
Acute Inhalation Toxicity	-	-
Skin Corrosive/irritant	-	-
Eye Damage/Irritation	-	-
Respiratory Sensitisation	-	-
Skin Sensitisation	-	-
Mutagenicity/Genotoxicity	-	-
Carcinogenicity	-	-
Reproductive Toxicity	-	-
Specific Target Organ Toxicity	-	-
Aspiration Toxicity	-	-

SPECIFICATIONS

Melting Point: -

Boiling point: 229 - 230°C

PURPOSE

Flavouring substance

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
5	25	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
Acceptable	JECFA	1998	No safety concern at current levels of intake when used as a flavouring agent.

FDA Status: [CFR21]

Section Number	Comments
172.515	Synthetic flavouring substances and adjuvant for the direct addition to food for human consumption.

HUMAN EXPOSURE

Natural Occurrence: It is reported to be a natural constituent of peppermint oil in varying amounts depending on the source. The synthetic product is

optically laevorotatory whilst the commercial product is optically inactive [Fenaroli, 2005].

Reported Uses: l-menthyl acetate is reportedly used in baked goods at 51.7 ppm, frozen dairy at 24.88 ppm, soft candy at 50.95 ppm, gelatin pudding at 40 ppm, non-alcoholic beverages at 2.59 ppm, alcoholic beverages at 2.1 ppm and hard candy at 10 ppm. Individual consumption has been reported to be 0.009138 mg/kg/day [Fenaroli, 2005].

TOXICITY DATA

In Vivo Toxicity Status

Test Type	Species	Route	Reported Dosage
LD_{50}	Rat	Oral	>5000 mg/kg
LD_{50}	Rabbit	Dermal	>5000 mg/kg
Irritation-Mild	Rabbit	Dermal	500 mg/24 hours. [Opdyke, 1976]

Dermal toxicity

When tested in human subjects the application of 8 % l-menthyl acetate in petrolatum for 48 hours under an occluded patch, produced no irritation. A maximisation test carried out on 25 human volunteers using l-menthyl acetate at 8% in petrolatum produced no sensitisation reactions [Opdyke, 1976].

Inhalation toxicity

The addition of menthyl acetate at 12 ppm to reference cigarettes, used in a 90 day-sub-chronic inhalation exposure in rats, led to a series of pathological changes to smoke exposure that were indistinguishable from those changes caused by the control cigarettes. This indicated that addition of menthyl acetate to a reference cigarette had no discernable effect upon the type or severity of the treatment related pathological changes associated with tobacco smoke exposure [Baker *et al.,* 2004].

Roemer (2014) and Schramke (2014) reported on a testing program designed to evaluate the potential effects of 350 ingredients added to an experimental kretek cigarette on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen [Ames assay] a mammalian cell cytotoxicity assay [neutral red uptake], Mouse Lymphoma assay, determination of smoke chemical constituents, a 4-day in vivo micronucleus assay and a 90-day rat inhalation study. Based on the results of these studies, the authors concluded that the addition of ingredients commonly used in the manufacture of kretek cigarettes, including menthyl acetate at levels up to 3 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Other relevant studies

Menthyl acetate is expected to be metabolised to menthol and a carboxylic acid. Metabolites of menthol are eliminated in the urine or faeces unchanged or conjugated with glucuronic acid. The ester hydrolysis is carried out by esterases or carboxylesterases, that occurs in most mammalian tissues but predominate in the hepatocytes [JECFA, 1999].

Behavioural data

Menthyl acetate injected intravenously in to mice was found to increase the ambulatory activity of mice at low doses, indicating a pharmacological activity on behaviour [Umezu *et al.,* 2001].

In Vitro Toxicity Status

Carcinogenicity and mutagenicity

Baker *et al.,* [2004]; examined the effects of the addition of 482 tobacco ingredients upon the biological activity and chemistry of mainstream smoke. The ingredients, essentially different groups of flavourings and casings, were added in different combinations to reference cigarettes. The addition of menthyl acetate at 12 ppm was determined not to have affected the mutagenicity of the total particulate matter (TPM) of the smoke in either the Ames, *in vitro* micronucleus assay or the neutral red assay when compared with that of the control cigarettes [Baker *et al.,* 2004].

The mutagenicity of the smoke condensate was assayed in the *Salmonella* plate incorporation [Ames] assay with the tester strain TA98 in the presence of an S9 metabolic activation system. The cytotoxicity of the cigarette condensate was determined in the neutral red uptake assay and the (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium, inner salt assay (MTS assay) with the human hepatocellular liver carcinoma cell line, HEP-G2. It was concluded that the *in vitro* mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients, which included menthyl acetate at levels up to 172 ppm [In vitro toxicity testing of tobacco ingredients in burnt form (Internal document R-46)].

Additional information concerning the *in vitro* mutagenicity of this material may be found in “An Interim report on data originating from Imperial Tobacco Limited’s Genotoxicity testing programme September 2003” or “An updated report on data originating from Imperial Tobacco Limited’s external Genotoxicity testing programme – Round 2 August 2007”.

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Other relevant studies

Menthyl acetate has been reported to be a moderately potent reversible inhibitor of cytochrome CYP3A4 activity in human liver microsomes [Dresser *et al.,* 2002].

PYROLYSIS AND TRANSFER STUDIES

No data identified

REFERENCES

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