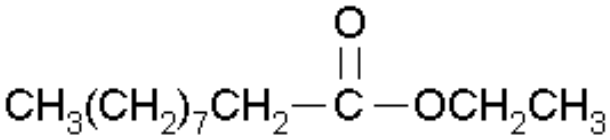
ETHYL DECANOATE

SYNONYMS

Ethyl caprate
Capric acid ethyl ester
Decanoic acid ethyl ester
Ethyl decylate
Ethyl decanoate (natural)

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_{12}H_{24}O_2$

IDENTIFIER DETAILS

CAS Number	:	110-38-3
CoE Number	:	309
FEMA	:	2432
EINECS Number	:	203-761-9
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: 241-242°C [Sigma-Aldrich, 2002]
Smiles code: C(CCCCCCCC)C(OCC)=O

PURPOSE

Flavouring substance.

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
2	10	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
ACCEPTABLE	JECFA	1996	No safety concerns at current levels of intake when used as a flavouring agent

FDA Status:[CFR21]

Section Number	Comments
C172.515	Synthetic flavoring substances and adjuvants

HUMAN EXPOSURE

Natural Occurrence: Ethyl decanoate is reported present in cognac, apples, butter chesses, grapes, pears, strawberries, wine, cocoa [Fenaroli, 1995; CoE, 2000].

Reported Uses: Ethyl decanoate is reportedly used in baked goods at 20.54 ppm, frozen dairy at 23.39 ppm, soft candy at 18.69 ppm, gelatin, pudding at 15.18 ppm, non-alcoholic beverages at 4.58 ppm, alcoholic beverages at 10.96 ppm, hard candy at 0.09 ppm, and chewing gum at 3.5 ppm [Fenaroli, 1995].

TOXICITY DATA

Carmines (2002), Rustemeier *et al.,* (2002), Roemer *et al.,* (2002) and Vanscheeuwijck *et al.,* (2002) reported on a testing program designed to evaluate the potential effects of 333 ingredients added to typical commercial blended test cigarettes on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen [Ames assay] a

mammalian cell cytotoxicity assay [neutral red uptake], determination of smoke chemical constituents and a 90-day rat inhalation study. Based on the findings of these studies, the authors concluded that the addition of the combined ingredients, including ethyl decanoate at levels up to <1 ppm, "did not increase the overall toxicity of cigarette smoke" [Carmines, 2002].

In Vivo Toxicity Status

Test Type	Route	Species	Reported Dosage
LD_{50}	Oral	Rabbit	> 5000 mg/kg
LD_{50}	Dermal	Rabbit	> 5000 mg/kg [Opdyke, 1976]
Irritation-Mild	Dermal	Rabbit	500 mg/kg/24 hr [Lewis, 2000].

Carcinogenicity and mutagenicity

Ethyl decanoate has been reported to have anti tumour activity, having protected AKR mice that were injected subcutaneously with transplantable AKR leukaemia cells at concentrations up to 5.0 mmol/ml together with the cell suspensions [Townsend *et al.,* 1961].

Dermal toxicity

Ethyl decanoate applied neat to either intact or abraded skin of rabbits occluded for 24 hours, was reported to cause erythema lasting for 24 hours [Levenstein 1976]. When tested at 2 % in petrolatum, in humans, it was reported to produce no irritation after 48 hours under an occluded patch [Kligman 1976]. When tested using the maximisation procedure at a concentration of 2 % in petrolatum, there was reported to be no sensitisation reactions in 25 human volunteers, [Kligman, 1976].

Inhalation toxicity

When tested at < 0.1 ppm in cigarettes, in a 13-week inhalation study, the presence of ethyl decanoate "…had no discernible effect on the character of extent of the biologic responses normally associated with inhalation of mainstream cigarette smoke in rats."[Gaworski *et al.,* 1998]. [However, it should be noted that the cigarettes had been spiked with a number of flavour ingredients in combination prior to smoking, and they contained a typical American blend humectant and sugar component (*i.e.* glycerine ≈ 20,000 ppm, propylene glycol at ≈ 24,000 ppm, and brown invert sugar at ≈ 24,000 ppm)] [Gaworski *et al.,* 1998].

A recent study investigated the effect of cigarettes, containing various additives in three combinations, in a 90-day nose-only smoke inhalation study

in rats. These ingredients included ethyl decanoate at < 1 ppm, a level described as a multiple of its typical use in a US cigarette. The data from this study, along with that from a number of other biological and chemical studies, indicate that the addition of the combined ingredients "did not increase the inhalation toxicity of the smoke, even at the exaggerated levels used" [Vanscheeuwijck *et al.,* 2002].

The addition of ethyl decanoate at 47 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 ethyl decanoate 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 Ethyl Decanoate at levels up to 267 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Reproductive and developmental toxicity

A group of four rats were reported to tolerate a choline deficient diet containing 35 % ethyl caprate for 14 days. At necropsy twice the control level of fatty acid was recovered from the livers of treated [Opdyke, 1976]. When ethyl caprate was fed to chicks at 5 % of the diet, it was reported to be digestible and palatable to chicks, with 100 % of the energy available for growth [Yoshida *et al,* 1968].

Ethyl decanoate is reported to inhibit the contractibility of frog skeletal muscle, but was reported not to affect serum calcium or blood serum levels in rabbits when injected subcutaneously at 500 mg/kg [Hano *et al.,* 1959].

Other relevant studies

Ethyl deconoate is reportedly metabolised in the gastrointestinal tract to decanoic acid and ethanol. The hydrolysis is catalysed by the classes of enzymes esterase or carboxylesterases, which in mammals are reported to occur throughout most tissues of the body, being predominantly found in hepatocytes [JECFA, 1998].

Ethyl caprate has been demonstrated to be a vehicle used to improve the percutaneous absorption of drugs [Hilton *et al.,* 1994].

Behavioural data

No data identified

In Vitro Toxicity Status

Carcinogenicity and mutagenicity

The mutagenicity of the smoke condensate with ethyl decanoate added to tobacco at 127 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. [In vitro toxicity testing of tobacco ingredients in burnt form (Internal document R-053)].

Roemer *et al.,* (2002) reported on a study in which cigarettes containing various additives in three different combinations were produced. Smoke condensates prepared from these cigarettes were then tested in two different *in vitro* assays. The mutagenicity of the smoke condensate was assayed in the *Salmonella* plate incorporation [Ames] assay with tester strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of an S9 metabolic activation system. The cytotoxicity of the gas/vapour phase and the particulate phase was determined in the neutral red uptake assay with mouse embryo BALB/c 3T3 cells. The authors concluded that the in vitro mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients which included ethyl decanoate at levels up to < 1 ppm [a multiple of its typical use in a US cigarette] [Roemer *et al.,* 2002].

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 ethyl decanoate at 47 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].

Ethyl decanoate was reported not to induce DNA damage in the rec assay using *B subtilis* H17 [rec +] and M45 [rec -] [Oda *et al.,* 1978; Yoo 1986].

Ethyl decanoate was reported to be 80% hydrolysed after incubation with a preparation of pancreatin for 2 hours [Grundschober, 1977].

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 Ethyl Decanoate at levels up to 267 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

REFERENCES

Baker RR, *et al.,* (2004) An overview of the effects of tobacco ingredients on smoke chemistry and toxicity. *Food Chem Toxicol*. **42** Suppl: S53-83

Carmines (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 1: Cigarette design, testing approach, and review of results. *Fd Chem Toxicol* **40**, 77-91.

CoE (2000). Council of Europe. Chemically-defined flavouring substances. Council of Europe Germany.

Fenaroli (1995) Fenaroli's handbook of flavour ingredients. Vol 2. 3rd Edition. CRC Press London.

Gaworski *et al.,* (1998). Toxicologic evaluation of flavor ingredients added to cigarette tobacco: 13-week inhalation exposure in rats. *Inhalation Toxicol*., **10**, 357-381.

Grundshober (1977). Toxicological assessment of flavouring esters. *Toxicology* **8:** 387-390.

Hano *et al.,* (1956) Pharmocolgical studies on some component of Coix Ma-yuen Stapf. I Studies on seed oil of Coix Ma-yuen Stapf *Yakugakuzasshi* **79:** 1412.

Hilton *et al.,* (1994). Vehicle effects on in vitro percutaneous absorption through rat and human skin. *Pharm Res* **11:** 1396-1400.

[In vitro toxicity testing of tobacco ingredients in burnt form (Internal document R-053)].

JECFA (1998) Safety evaluation of certain food contaminants. Prepared by the forty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives. IPCS Geneva.

Kligman (1966). Report to RIFM [As cited in Opdyke 1976].

Lewis (2000). Sax's dangerous properties of industrial chemicals. 10th Edition Vol 2 John Wiley & Sons Inc. New York.

Oda *et al.,* (1978). Mutagenicity of food flavours in bacteria. *Shokuhin Eisei Hen* **9:** 177-181.

Opdyke (1976). Monographs on fragrance raw materials: Ethyl caproate *Fd Cosmet Toxicol.* **14:** 761-762.

Roemer (2014) Toxicological assessment of kretek cigarettes: Part 1: background, assessment approach, and summary of findings. Regul Toxicol Pharmacol.; **70** Suppl 1: 2-14.

Roemer (2014) Toxicological assessment of kretek cigarettes Part 6: the impact of ingredients added to kretek cigarettes on smoke chemistry and in vitro toxicity. Regul Toxicol Pharmacol.; **70** Suppl 1: 66-80.

Roemer *et al.,* (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 3: In vitro genotoxicity and cytotoxicity. *Fd Chem Toxicol* **40**, 105-111

Rustemeier *et al.,* (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 2: Chemical composition of mainstream smoke. *Fd Chem Toxicol* **40**, 93-104.

Schramke (2014) Toxicological assessment of kretek cigarettes. Part 7: the impact of ingredients added to kretek cigarettes on inhalation toxicity. Regul Toxicol Pharmacol; **70** Suppl 1: 81-9.

Townsend *et al.,* (1961). Studies on the *in vitro* antitumor activity of fatty acids IV. The esters of acids closely related to 10-hydroxy-2-decanoicacid from royal jelly against transplantable mouse leukaemia *Can J Bio Chem Physiol* **39:** 1765.

Sigma-Aldrich, (2002). Obtained from http://www.Sigmaaldrich.com

Vanscheeuwijck *et al.,* (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 4: Subchronic inhalation toxicity. *Fd Chem Toxicol* **40**, 113-131.

Yoshida (1970). Availability of energy in esters of aliphatic acids and alcohols by growing chicks. *Agric Biol Chem* **34:** 1668.

Yoo (1986). Mutagenic and anti mutagenic activities of flavouring agents used in food stuffs. *J Osaka Cy Med Cent* **34:** 267.