ETHYL PROPIONATE

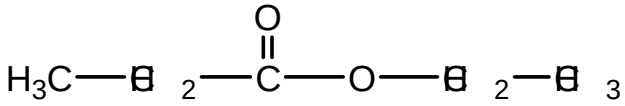
SYNONYMS

Propanoic acid, ethyl ester
Ethyl n-propanoate
Ethyl propionate(Nat C-3 Ethyl Ester)
Ethyl propanoate
Ethyl propionate (natural)
Propionic ester

CHEMICAL FORMULA

$C_5H_{10}O_2$

CHEMICAL STRUCTURE



IDENTIFIER DETAILS

CAS Number	:	105-37-3
CoE Number	:	402
FEMA	:	2456
EINECS Number	:	203-291-4
E Number	:	-

SPECIFICATIONS

Melting Point: -99 C

Boiling point: 210 C at 0 mmHg

PURPOSE

Flavouring substance.

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
10	80	100 alcoholic beverages

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
ACCEPTABLE	JECFA	1996	No safety concern at current levels of intake

FDA Status: [CFR21]

Section Number	Comments
C172.515	Synthetic flavoring substances and adjuvants

HUMAN EXPOSURE

Natural Occurrence: Ethyl propionate is reported found in several types of wine, in white wine grape var. *Sauvignon*, in cocoa, various cheeses and fruit juices (apple; orange; grapefruit; guava); melon; peach; strawberry; tomato; beer ;cognac; rum; whisky; kiwi fruit and mussels [Fenaroli, 2005].

Reported Uses: Ethyl propionate is reportedly used in baked goods at 84.72 ppm, fats, oils at 0.1 ppm, frozen dairy at 49.47 ppm, meat products at 1.5 ppm, soft candy at 53.52 ppm, soft candy at 53.52 ppm, gelatin pudding at 33.66 ppm, non-alcoholic beverages at 19.92 ppm, alcoholic beverages at 83.47 ppm, gravies at 4 ppm, hard candy at 77.04 ppm, and chewing gum at 678.7 ppm [Fenaroli, 2005].

Ethyl propionate has been in use since the 1930 's. It has been used in soap at a level of 0.01%, in detergent at 0.01%, in creams/lotions at 0.03%, and in perfume at 0.4% [Opdyke, 1978]. The estimated per capita intake is 0.09816 mg/kg [Fenaroli, 2005].

Dissolution of gallstones has been carried out in humans using ethyl propionate as the solvent [Clerici *et al.,* 1997].

TOXICITY DATA

DEREK failed to identify any alerts within the structure of ethyl propionate.

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 propionate at levels up to 59 ppm, "did not increase the overall toxicity of cigarette smoke" [Carmines, 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 propionate at 316 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].

Renne *et* al., (2006) evaluated the effects of tobacco flavouring and casing ingredients on both mutagenicity, and a number of physiological parameters in Sprague-Dawley (SD) rats. Test cigarettes containing a mixture of either 165 low-uses or eight high-use flavouring ingredients which included ethyl propionate at 1.3 ppm, were compared to a typical commercial tobacco blend without flavouring ingredients. The Ames assay (TA 98, 100,102, 1535 and 1537 ±S9) did not show any increase in Mutagenicity from "low" or "high" cigarette smoke condensate compared to the control. SD rats were exposed by nose-only inhalation for 1h/day, 5 days/wk for 13 weeks to smoke at concentrations of 0.06, 0.2 or 0.8mg/L from the test or reference cigarettes, or to air only. Plasma nicotine, COHb and respiratory parameters were measured periodically. Rats were necropsied after 13wk of exposure or following 13 wk of recovery from smoke exposure. Biological endpoints assessed included; clinical appearance, body weight, organ weights, and lesions (both gross and microscopic). The results of these studies did not indicate any consistent differences in toxicological effects between smoke from cigarettes containing the flavouring or casing ingredients and reference cigarettes [Renne *et al.,* 2006].

In Vivo Toxicity Status

Test Type	Route	Species	Reported Dosage
LD_{50}	oral	rat	3500mg/kg
LD_{50}	oral	rat	8732mg/kg [RTECS]
LD_{50}	oral	rabbit	3200-3900mg/kg
LD_{50}	*i.p.*	mice	1300mg/kg
LD_{50}	*i.p.*	rat	1200mg/kg
LD_{50}	dermal	rat	>5000 mg/kg [Opdyke, 1978]
LDL_0	Skin	rabbit	14256mg/kg [RTECS]
LD_{50}	oral	rabbit	5700mg/kg [Iba, 1965].
LD_{50}	i.p.	mouse	1158mg/kg [ToxNet, 2010].

Listed in the HSDB as part of the TSCA test submission was a short summary of an unreviewed acute oral rat study. Male and female rats were administered (per oral) 4.0 (n=2), 8.0 (n=5), 11.3 (n=5), and 16.0 (n=5) mg/ kg bw. Female rat data was not provided but male rat data were described as follows;

"In male rats, treatment was associated with sluggishness, prostration, and mortality at approximately 15 minutes to 3 hours post-dosing. A solitary male died after 1 day . Only males of the 2 highest dose levels succumbed or demonstrated recorded toxic effects throughout 14-day observation. An acute oral LD50 for male rats was 10.8 mL/kg bodyweight; a female LD_{50} was 9.8 mL/kg. The survivors recovered fully within 1 to 2 d ays. Upon necropsy, apparent treatment-related pathology among male rats was limited to the

study decedents; gross lesions included dark red and mottled lungs, white to grey stomachs, liquid-filled stomachs and intestines, red or white intestine, and spotty white to grey or red kidneys".

[HSDB, 2010]

Dermal toxicity

Neat ethyl propionate is a moderate rabbit skin irritant, although at the concentration of 2% in petrolatum, in a volunteer study, it was neither an irritant nor sensitizer of human skin (48 hour closed patch) [Opdyke, 1978].

Listed in the HSDB as part of the TSCA test submission was a short summary of an unreviewed acute dermal rat study. Male and female rats (5/sex/group) were administered a single dose (percutaneously) of 16ml/kg bw for 24 hours. Results were described as follows;

"Treatment was associated with death of a solitary female at 11 days post-treatment. Local reactions were characterized by erythema, edema, ecchymosis, necrosis, desquamation, fissuring, ulceration, alopecia, and scabbing. The female succumbing was emaciated at death; however, no signs of systemic toxicity were observed in the survivors (9/10) of 14-day post-treatment observation. Upon necropsy, the decedent female also exhibited bright red lungs. No gross lesions were identified in study survivors. Procedural appendices were not included with this submission and no further information regarding method or results was provided".

[HSDB, 2010]

Inhalation toxicity

Ethyl propionate vapour has been described as having a narcotic effect on rats (concentration in air not given but NISC (2002) references 15000 ppm, mean exposure time for narcotic effect to occur was 2503 seconds) [Opdyke, 1978].

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 propionate at 59 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 propinoate at 316 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 propinoate 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].

Listed in the HSDB as part of the TSCA test submission was a short summary of an unreviewed acute inhalation rat study. Male and female rats (5/sex/group) were 'exposed under static conditions to a substantially saturated vapour for 11.2, 22.5 and 45 minutes'. Results were described as follows;

"Four of 5 males and 5/5 females died during 45-minute exposures, the treatment-related mortality consistent with LT50's (with 95% confidence limits) of 35 (26-47) and 32 (23-44) minutes, respectively. Clinical signs of toxicity, observed both during and after the exposures, included labored breathing, wetness of periocular and perioral fur, hypoactivity, lacrimation, slowed breathing, ataxia, slow or negative surface righting reflex, and negative toe and tail pinch reflex. The survivors of all exposure levels recovered within 1 day post-exposure. Following 14-day observation, terminal necropsy of these animals revealed no gross lesions attributable to treatment. Conversely, red lungs, wetness or red discharge of perinasal and/or perioral fur, gas-filled stomachs, and liquid-filled trachea were observed among the study lethalities. Procedural appendices were not included with this submission and no further information regarding method or results was provided".

[HSDB, 2010]

Behavioural data:

No data identified

***In Vitro* Toxicity Status**

Carcinogenicity and mutagenicity

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".

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 ethyl propionate at levels up to 42 ppm.

A total of 95 ingredients were tested individually through addition at different concentrations to the tobacco of experimental cigarettes. Mainstream cigarette smoke chemistry analysis, bacterial mutagenicity testing, and cytotoxicity testing were conducted. The authors concluded that these ingredients, which included ethyl propionate applied at levels up to 10000 ppm on cigarettes

produced minimal changes in the overall toxicity profile of mainstream cigarette smoke, and in some cases, the addition of high levels of an ingredient caused a small reduction in toxicity findings, probably due to displacement of burning tobacco [Gaworski *et al*., 2011].

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 propionate at levels up to 59 ppm (a multiple of its typical use in a US cigarette) [Roemer *et al.,* 2002].

When tested in the Ames assay with *Salmonella typhimurium* TA92, TA1535, TA100, TA1537, TA97, and TA 98, ethyl propionate was negative at concentrations up to 50 mg/plate, with and without S9 [Ishidate *et al.,* 1984].

Ethyl propionate was negative in a chromosomal aberration test with a Chinese hamster fibroblast cell line (CHL), at dose concentrations up to 2 mg/ml [Ishidate *et al.,* 1984].

Ethyl propionate was negative in a Chinese hamster lung fibroblast cell line in a clastogenicity assay at doses up to 2000 g/ml in the absence of a rat liver S9 activation fraction [Ishidate *et al.,* 1988].

Ethyl propionate was negative in a Rec assay with *Bacillus subtilis* strains H17 and M45, when tested at concentrations up to 18 µg/disk [Oda *et al.,* 1978].

Pure ethyl propionate [up to 9.69 mg/ml] was found to marginally induce mitotic chromosome loss in *Saccharomyces cerevisiae* . However, in the presence of propionitrile (11.6 or 15.4 mg/ml), ethyl propionate (up to 4.37 mg/ml) was found to strongly induce chromosome loss [Zimmermann *et al.,* 1989].

At levels up to 1.04%, ethyl propionate was found to be a weak inducer of aneuploidy in *Saccharomyces cerevisiae* [Zimmermann *et al.,* 1985].

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".

Other relevant studies

Ethyl propionate at lethal doses to rats, had symptoms of ataxia and hypothermia due to production of propionic acid [Opdyke, 1978].

Ethyl propionate exposure in laboratory animals may lead to gastrointestinal irritation and degenerative changes in the heart, kidneys and liver [Opdyke, 1978].

Ethyl propionate was identified as less cytotoxic on intestinal mucosa that methyl tert-butyl ether for topical gallstone dissolution. Ethyl propionate was also identified as more effective for gallstone dissolution [Zakko *et al.,* 1997].

In an experiment investigating the toxicity of gallstone solvents, ethyl propionate was infused intraduodenally to male New Zealand rabbits. The rabbits were infused at a rate of 8.5 µl/min or 4.0 µl/min. Biochemical analysis of the blood found no significant changes in serum alkaline phosphatase, amylase, or bilirubin. There were no significant changes in their hepatic histology or histologic scoring for mucosal necrosis and ulceration. Ethyl propionate did produce a significantly higher level of aminotransferases. In their discussion, the authors state that direct intraduodenal exposure of ethyl propionate can produce submucosal inflammation [Clerici *et al.,* 1997].

Esch *et al*. (1992) stated that ethyl propionate met certain criteria identifying it to be suitable for contact dissolution of gallstones. Namely, it dissolved cholesterol gallstones rapidly, "should not cause local tissue injury, should not have systemic toxicity …". In an experiment involving rabbits and piglets, gallbladder mucosal injury was assessed following ethyl propionate irrigation. New Zealand White Rabbits received ethyl propionate via a transhepatic catheter for 2 hours (a dose of 0.5-1.5 ml replacing aspirated bile). Histological assessment of the gall bladder revealed severe mucosal injury including necrosis of cells at the villus tips immediately after the 2-hour exposure. Four days after exposure the injury had decreased, and was completely healed after 8 days. In a similar study, piglets received ethyl propionate through a computerised syringe pump and catheter (a dose of approximately 5 ml replacing aspirated bile). Again severe mucosal injury was evident immediately after exposure and this was healed after 8 days [Esch *et al.,* 1992].

Ethanol is the main metabolite of ethyl propionate [species not given] following hydrolysis that also yields propionic acid. Assuming complete absorption and hydrolysis, 1 ml of ethyl propionate will produce approximately 0.5 ml ethanol [Clerici *et al.,* 1997].

The partition coefficient (n-octanol/water) Log K_{ow} for ethyl proionate was reported to be 1.21. [http://www.vet.utk.edu/TETRATOX/pdf/AliphaticToxicityTable.pdf

Listed in the HSDB as part of the TSCA test submission was a short summary of an unreviewed primary dermal irritation rabbit study. Male and female rabbits (3/sex) were exposed to 0.5mL via occluded percutaneous applications over 4 hours. Results were described as follows;

"A solitary female died of unknown causes at 7 days post-treatment; the

mortality could not be related to treatment. No further indications of irritation or systemic effects were observed in any animal during 7-day post-treatment observation. Procedural appendices were not included with this submission and no further information regarding method or results was provided".

Also listed was a rabbi t eye irritation study. Six rabbits were given a 0.1mL instillation into a single eye. Results were described as follows;
"By 4 hours post-instillation, iritis, moderate conjunctival irritation, with marked discharge were apparent in all treated eyes. With in 24 hours, 2/6 eyes appeared normal, while the rest displayed slight persistent conjunctival redness. All eyes were clear of any sign of irritation by 48 hours post-instillation. Procedural appendices were not included with this submission and no further information regarding method or results was provided".

[HSDB, 2010]

PYROLYSIS AND TRANSFER STUDIES

Information relating to the pyrolysis and/or transfer of ethyl propionate is detailed in the Report on Thermochemical Properties of Ingredients document. In the aforementioned document, the term 'pyrolysis' means the heati ng of an ingredient in isolation under controlled conditions in an analytical device to examine its degradation potential. The expression 'transfer data' on the other hand is used to describe the fate of an ingredient in qualitative and quantitative terms following the smoking of a tobacco product to which it has been applied.

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