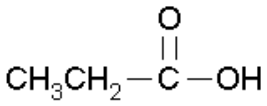
PROPIONIC ACID

SYNONYMS

Ethyl formic acid
Methyl acetic acid
Propanoic acid

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_3H_6O_2$

IDENTIFIER DETAILS

CAS Number	:	79-09-4, 29497-08-3 (polymer)
CoE Number	:	3
FEMA	:	2924
EINECS Number	:	201-176-3
E Number	:	

CLP CLASSIFICATION

Ingredient CLP Classification: Yes

Endpoint	Classification	Category
Acute Oral Toxicity	conclusive but not sufficient for classification	-
Acute Dermal Toxicity	conclusive but not sufficient for classification	-
Acute Inhalation Toxicity	conclusive but not sufficient for classification	-
Skin Corrosive/irritant	H314: Causes severe skin burns and eye damage.	1B
Eye Damage/Irritation	H318: Causes serious eye damage.	1
Respiratory Sensitisation	conclusive but not sufficient for classification	-
Skin Sensitisation	conclusive but not sufficient for classification	-
Mutagenicity/Genotoxicity	conclusive but not sufficient for classification	-
Carcinogenicity	conclusive but not sufficient for classification	-
Reproductive Toxicity	conclusive but not sufficient for classification	-
Specific Target Organ Toxicity	Single Exp. H335: May cause respiratory irritation	3
Aspiration Toxicity	conclusive but not sufficient for classification	-

REACH Statement

This ingredient has been registered under REACH. Under REACH, registrants have an obligation to provide information on substances they manufacture or import. This information includes data on hazardous properties (covering various toxicological endpoints), guidance on safe use and classification and labelling. The European Chemicals Agency (ECHA) makes this information publicly available on its website: http://echa.europa.eu/.

SPECIFICATIONS

Melting Point: -21.5 °C (Chemfinder, 2002).
Boiling point: 140.7 °C (Chemfinder, 2002).

PURPOSE

Flavouring substance.

STATUS IN FOOD AND DRUG LAWS

CoE limits:

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

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
Not limited	JECFA	1997	No safety concern at current level of intake,

			when used as a flavouring agent

FDA Status: (CFR21)

Section Number	Comments
184.1081	Direct food substance GRAS - Propionic acid

HUMAN EXPOSURE

Natural Occurrence: Propionic acid is reportedly found in apple, apple juice, beef, beef broth, beer blackberry juice, bread, cheese, cherry juice, roasted cocoa bean, cocoa powder, coffee, cognac, blackcurrant juice, white currant juice, grape juice, grape musts and wine, grapefruit juice, maple syrup, raw milk, orange juice, Valencia orange oil, orange essence, roasted peanuts and other natural sources [Fenaroli, 2005].

Propionate is a normal intermediary metabolite formed as the terminal three-carbon fragment (as propionyl-coenzyme A) in the oxidation of odd-number carbon fatty acids and from the oxidation of the side chain of cholesterol. The metabolism of propionic acid involves interaction with coenzyme A, carboxylation to form methylmalonyl-coenzyme A and conversion to succinic acid, which enters the citric acid cycle. Radioactivity from administered, propionate may appear in glycogen, glucose, citric acid cycle intermediates, amino acids and proteins. In man, propionic acid composes up to 4% of the normal, total plasma fatty acid [Guest, *et al.,* 1982].

Reported Uses: Propionic acid is reportedly used (maximum levels) in baked goods at 0.12 ppm, fats and oils at 0.07 ppm, frozen dairy at 0.01 ppm, soft candy at 0.01 ppm, non-alcoholic beverages at 0.01 ppm, and imitation dairy at 0.06 ppm [Fenaroli, 2005].

Swiss cheese 90-7030 mg/kg; fish 3-4 mg/kg, vinegar 82-25000 mg/kg; beer 1.3-5 mg/kg and coffee 49.6-125.8 mg/kg, [COE, 2000].

Demand for propionic acid was 130 million pounds by 1992, with current use as follows: grain and feed preservatives (25 %), cellulose plastics (20 %), calcium and sodium propionates (18 %), herbicide manufacture (18 %), exports (15 %) and miscellaneous uses, including butyl and pentyl propionates (4 %). Butyl and pentyl propionates may be up to half of the growing market in the paint and coatings industries in the future. Consequently propionic acid may be released in to the environment via effluents where it is produced or used. Propionic acid is also released into the environment via effluents from the manufacture and use of coal-derived and shale oil liquid fuels, the disposal of coal liquefaction and gasification waste by products, and wood preserving chemical waste by products. Propionic acid may also be released into the aquatic environment in waste water discharges from textile mills and sewage treatment facilities. Municipal and industrial landfills and hazardous waste sites via leachates can release propionic acid to ground water supplies. Propionic acid can be emitted to air as a component if exhaust from gasoline and diesel fuelled engines [Howard, 1997].

TOXICITY DATA

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 propionic acid at 13 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 1 h/day, 5 days/wk for 13 weeks to smoke at concentrations of 0.06, 0.2 or 0.8 mg/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.

In Vivo Toxicity Status

Species	Test Type	Route	Reported Dosage
Mouse	LD_{50}	Oral	2600-5760mg/kg
Rabbit	LD_{50}	Dermal	500µl/kg
			[BIBRA profile, 1991].
Rat	LD_{50}	Peritoneal	3500mg/kg
Mouse	LD_{50}	Intravenous	625mg/kg
Rabbit	LD_{50}	Intravenous	1320mg/kg
			[Sax, 1985].
Rat	TD_{LO}	Oral	14g/kg (7 days)
Rat	TD_{LO}	Unreported	4598mg/kg (9 weeks)
Mouse	TD_{LO}	Oral	33600mg/kg (7 day)
Hamster	TD_{LO}	Oral	42g/kg
Rat	TC_{LO}	Inhalation	23mg/m3 (30 days)
			(Sax, 1995).

A study in which five male and five female rats, mice and hamsters were fed a diet containing 4 % propionic acid for 7 days revealed evidence of damage and cellular proliferation in the epithelium of the forestomach and limiting ridge in all three species of rodents. Tumours observed in the forestomach of rats after long-term feeding programmes are thought to be the consequence of continued damage and repair, [Harrison, *et al*., 1991]

Rats on a diet containing propionic acid at (4 %) ~2.7 g/kg bw/day, showed an increased thickening of the forestomach (at 21 days). The appearance of

ulcers, overt damage to the stomach lining and an increase in the number pf cells in the forestomach was observed in another study after a 20 week period. This study also reported stomach injury when propionic acid was administered at a dietary concentration of 0.4 % [BIBRA profile, 1991].

The administration of propionic acid to rats (in the diet) in combination with 13 other additives at a maximum propionic acid concentration of 1.67 % (~ 1g/kg bw/day), reported blood changes, decreased growth, increased liver weight and mild liver damage in female rats at the maximum dose, [BIBRA profile, 1991]

Deaths were reported in a study in which rats on vitamin B_{12} deficient diets fed 1.95 % propionic acid (~1 g/kg bw/day, 4 weeks. No group size or species details were given), [BIBRA, 1991].

Twelve monkeys receiving a diet containing 2 % sodium proionate (~0.42 g/kg bw/day-9 weeks). Apparently showed no toxic effects (this study only examined blood and liver effects with no other details given) [BIBRA profile 1991].

Dogs fed with propionic acid (dose not specified) for a 90 day period showed hyperplasia of the oesophagus possibly indicating that propionic acid could mechanically irritate oesophageal tissue [EPA, 1989].

Propionic acid was reported to have a NOEL (no-observed-effect-level) in rats of 1 mg/kg bw/day in a six-month study (doses used throughout the study were not stated) [Leung *et al*., 1990].

Carcinogenicity and Mutagenicity

A recent mouse skin painting study investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including propionic acid at 0.1 ppm. The authors concluded that the study "did not indicate any substantive effect of these ingredients on the tumorigenicity of cigarette smoke condensate" (Gaworski *et al.*, 1999). (It should be noted that the cigarettes 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)).

It has been reported that three out of four mixed strain male and female rats (50-80 g bw) that had been fed a diet of 5 % propanoic acid (~5 g per kg) developed 'warty' lesions of the forestomach after 110 days. Histopathology examination revealed there was no evidence of infiltrative malignant growth (FDA report 1979). However, preliminary data from a study in which propionic acid was administered in the diet at 4 % (~2.7 g/kg bw/day) benign tumours of the forestomach were apparent after 20 weeks. As propionic acid gave negative results in mutagenicity assays it is reported that tumours are not likely to be due to a direct attack on DNA) [BIBRA profile, 1991].

Dermal toxicity

The direct contact of aqueous propionic acid solutions (up to 15 % w/w) did not cause any irritation to human skin, however, the concentrated acid was reported to be a moderate irritant which after initial stinging is reported to produce skin hyper-pigmentation, [Consensus report for propionic acid, 1987].

Propionic acid was reported to give a severe eye irritant response in adult rabbits, (990μg) [Sax, 1995].

Solutions of propionate applied to the eye (in man and rabbits) at concentrations up to 15 and 20 % respectively, had no irritating effects (JECFA, 1974). However, a 5 % solution of the acid was reported to produce severe corneal damage in rabbits, and a 20 % solution of the sodium salt was reported to produce transient burning and redness, [BIBRA profile, 1991].

Propionic acid was also noted to be a moderate skin irritant, which on application caused a stinging pain followed by hyper-pigmentation of the skin, (JECFA, 1974). A skin irritation study carried out in rabbits (4 hour closed contact study) indicated that at 2.5 % (aqueous solution of the acid), produced a mild irritant effect, mild/moderate irritation was observed at 25 % solutions and severe irritant/corrosion was seen at concentrations of 40 % and above.
A primary skin irritation study (rabbit), revealed that propionic acid was a severe skin irritant at 495 mg, (no other details given) [Sax, 1995].

A skin corrosion study in which six New Zealand rabbits, where clipped of all hair on the backs and flanks 24 h prior to application of propionic acid (15 %) revealed a negative result after application to designated patch areas for a 4 hr period, [Vernot *et al*., 1977].

Administration by injection of 0.55-2.2 g/kg bw propionic acid (i.v. 14 %) rabbits or dogs, and 1 g/kg (subcutaneous) cats produced reversible effects on the nervous system, (no particular effects stated), [BIBRA profile, 1991].

Propionic acid when administered continuously or in pulses into the rumen of dairy cows (intragastric infusions) was observed to produce peaks in the levels of insulin which corresponded to the pulse of propionic acid, [Sax, 1995].

Reproductive Toxicology

Species	**Concentration**	**Duration**
Mice and rats	up to 300 mg/kg bw/day	10 days
Rabbits	up to 400 mg/kg bw/day	13 days
Hamster	up to 400 mg/kg bw/day	5 days

The previous treatments produced no treatment related effects on litter size, foetal survival or number of foetal abnormalities [BIBRA profile, 1991].

The reported daily *per capita* Intake 'eater only' for propionic acid in the USA and Europe was 86 and 19 μg/kg bw/dy respectively. It was also noted as endogenous to humans and reported to be of no safety concern at the current levels of intake, [WHO, 1998].

Inhalation toxicity

Exposure of rats to a saturated atmosphere of propionic acid (conc. not given) or an 8 hr period caused no deaths. Rats exposed to atmospheres containing up to 5 mg/l of propionic acid (4-hr exposure) were observed to have slight eye irritation during and for several hours after exposure. Another study also reported slight nasal irritation under the above conditions [BIBRA profile, 1991].

Medical reports of acute exposures of workers to propionic acid revealed mild to moderate skin burns, mild eye redness and a single case of a mild cough and asthmatic response [Sax, 1985].

There were no OSHA (Occupational safety and health) regulations on the inhalation limit to propionic acid. However, the American Conference of Governmental Industrial Hygienists has recommended a threshold limit value (time weighted average concentration of a substance to which most employees can be exposed without any adverse effect) of 30 mg/m^3, 10 ppm (Sax. 1995). Atmospheric concentrations of 0.25-2.1 ppm were noted to be non-irritant, however there has been one reported case of propionic acid in the atmosphere causing mild coughing and an 'asthmatic' response (as stated in first paragraph, [BIBRA profile, 1991].

A study designed to determine occupational exposure limits to propionic acid involved 30 healthy adults aged 17-41 yrs (air temp 20-21^{o}C and relative humidity of 50-70 %) gave a threshold of smell value 0.078 mg/m^3. Subjects were exposed to propionic acid at concentrations of, 5000, 2000, 800, 100 and 23 mg/m^3 (exposure in triplicate). The no effect concentration level was observed to be 0.02 mg/m^3. The clinical picture of acute intoxication was also reported as part of the study and was conducted in rodents and reported to be characterised by limpness, sluggishness, irritation of the upper respiratory tract and discharge from the nasal tracts), [Tokanova, 1982].

Twelve rats were exposed to concentrations of 5000, 2000, 800, 100 and 13 mg/m^3. At 5000 and 2000 mg/m^3 brief excitation followed by a 'limpness' in the animal was observed, no behaviour changes were observed at the other concentrations. Weight changes throughout the study were not statistically different from those of the control group however, a decrease in erythrocyte and haemoglobin levels in the blood occurred at all concentrations of propionic acid, with changes in leukocyte count not being statistically reliable. Treatment related changes in the internal organs were most pronounced for the lungs (plethora of the vessels, emphysema). Peribronchitis and bronchitis was reported to develop at relatively low concentrations of propionic acid, (exact concentrations not stated), [Tokanova, 1982].

The addition of propionic acid 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 propionic acid 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].

When tested at <0.1 ppm in cigarettes, in a 13-week inhalation study, the presence of propionic acid 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].

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 propionic acid at levels up to 57 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Behavioural data

Long-Evans hooded rats received intracerebroventricular injections of propionic acid (PPA) or control compounds prior to behavioural testing in water maze and beam tasks. PPA-treated rats were impaired in the water maze task which was indicated by an unusual pattern of mild or no impairment during spatial acquisition training, but marked impairment during spatial reversal training. PPA-treated rats were also impaired on the beam task. Neuropathological analysis from PPA-treated rats revealed an innate neuroinflammatory response. The authors concluded that PPA can change the brain and behaviour in the laboratory rat which are consistent with symptoms of human autism [Schultz et al., 2009].

Rats given propionic acid via intraventricular infusions demonstrated reversible repetitive dystonic behaviours, hyperactivity, turning behaviour, retropulsion, caudate spiking, and the progressive development of limbic kindled seizures and it was concluded that propionic acid may have central effects. Propionic acid treated rats also showed an increase in oxidative stress markers and biomarkers indicative of neuroinflammatory process. It is

suggested that altered propionic acid metabolism may be associated with some types of autism [MacFabe *et al.,* 2007].

In Vitro Toxicity Status

Carcinogenicity and Mutagenicity

Mutagenicity studies: Ames test *S.typhimurium* (Strain TA100, TA-1535, TA-1537, TA-1539, and TA-98) with and without metabolic activation were negative (100-500μg /plate). Assays using *S.cerevisiae* (yeast strain D-4) were also negative [FDA report 1979; BIBRA profile, 1991].

A later Ames study also produced negative results with *S. typhimurium* (Strain TA 97, 98, 100, 1535, 1537) at dosages between 100-6667 μg/plate (solvent: distilled water) without metabolic activation. Further experiments revealed that these strains also gave negative results in the presence of metabolic activation (both hamster (Syrian) and rats (Sprague-Dawley) liver, S-9, Aroclor 1254) at 100-10,000 μg/plate, (S-9 mixes contained 10 or 30 % S-9 however, results for TA1537 only contained 30 % S-9) [Zeiger, *et al*., 1992].

Propionic acid when analysed in the *E. coli,* DNA repair assay, (strains WP2, WP67 *uvr*A$^-$, *pol*A$^-$ and CM871 *uvr*A$^-$, *rec*A$^-$ and *lex*A$^-$ at 1,5 and 25 μl) SOS chromotest, (0.01, 0.03, 0.1, 0.3, 1.0, 3.3 mM in the absence and presence of metabolic activation), *Salmonella*/microsome mutagenicity test, (TA98, TA100 TA1535 and TA1537 in the absence and presence of activation at 0.01, 0.03,0.1,0.3, 0.1, 3.3 and 10 μl/plate),sister chromatid exchange test *in vitro* (using hamster V9 cells in the absence and presence of activation at 0.1,0.3,1.0, 3.3, 10, 33.3 mM) and the micronucleus test *in vivo*, (2.5 % in the bone marrow cells of Chinese hamsters after the intraperitoneal injection of propionic acid). All tests except the DNA repair assay with *E.coli* gave negative results, [Basler *et al.,* 1987].
Propionic acid did not induce DNA damage in *E.coli*, with or without metabolic activation (no dose given) [BIBRA profile, 1991].

Propionic acid (2.5 mM) increased sister chromatid exchange (SCE) in cultured (72 h) human lymphocytes with a 48 h treatment, starting at 24 h after culture initiation, (propionic acid affected medium pH only slightly with a maximum drop of 0.2 pH units) at the concentration that induced SCE. The response was less than 1.8 times higher than the mean number of SCEs in the control cultures, [Sipi *et al*., 1992].

Fu *et al.,* 2004 stated that short-chain fatty acids (SCFA) in the colon may maintain colonocyte differentiation and oppose carcinogenesis. The authors investigated the effects of three SCFA, butyrate, propionate and acetate, on the differentiation, proliferation, and matrix interactions of the Caco-2 human colonic adenocarcinoma cell line. All three SCFA studied altered the Caco-2 phenotype. Treatment with 10 mmol SCFA significantly prolonged the cell doubling time, promoted brush border enzyme expression (cathepsin C), and inhibited the motility of the Caco-2 cells. It was concluded that butyrate, propionate and acetate inhibited the proliferation and motility of a well-

differentiated human colonic cancer cell line while promoting the expression of the differentiation marker, cathepsin C. Thus the SCFA produced by bacterial fermentation of dietary fiber may exert a protective effect against the development of colon cancer [Fu *et al.,* 2004].

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 propionic acid 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].

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 *propionic acid* at levels up to 41 ppm.

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 propionic acid at levels up to 57 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

PYROLYSIS AND TRANSFER STUDIES

Information relating to the pyrolysis and/or transfer of propionic acid is detailed in the Report on Thermochemical Properties of Ingredients document. In the aforementioned document, the term 'pyrolysis' means the heating 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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