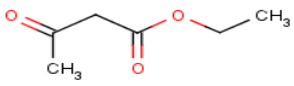
Ingredient synonym names

IDENTIFIER DETAILS

CAS Number	FEMA Number	Additive Number	Ingredient EC Number	Ingredient chemical structure
141-97-9			205-516-1	

CAS Additional Number	FL Number	CoE Number

Chemical formula	C6-H10-O3

Ingredient CLP Classification

Ingredient REACH Registration Number
01-2119457642-36

Acute Oral Toxicity	Eye Damage/Irritation	Carcinogenity
0	0	0

Acute Dermal Toxicity	Respiratory Sensitisation	Reproductive Toxicity
0	0	0

Acute Inhalation Toxicity	Skin Sensitisation	Aspiration Toxicity
0	0	0

Skin Corrosive/Irritant	Mutagenicity/ Genotoxicity	Specific Target Organ Toxicity
0	0	0

SPECIFICATIONS

Melting Point	- 45°C	Boiling Point	180.8°C

STATUS IN FOOD AND DRUG LAWS

Acceptable Daily Intake (ADI, mg/kg)	Acceptable
Acceptable Daily Intake (ADI) comments	No safety concern at current levels of intake when used as a flavouring agent - JEFCA (1999)

FDA Status					
CoE limits - Beverages(mg/kg)	50	CoE limits - Food (mg/kg)	50	CoE limits - Exceptions (mg/kg)	-

HUMAN EXPOSURE

Ingredient Natural Occurence (if applicable)

Occurs in strawberry, coffee, passion fruit juice (yellow), babaco fruit and bread [Fenaroli, 2005].

References - Ingredient Natural Occurence

Fenaroli (2005). Fenaroli's Handbook of Flavour Ingredients, 5th Edition. CRC Press, Boca Raton, USA.

Ingredient Reported Uses

Ethyl acetoacetate is reportedly used in breakfast cereals at 100 ppm, frosting on confection at 800 ppm, fruit ices at 100 ppm, fruit juice at 1 ppm, jams and jellies at 980 ppm, milk products at 100 p pm, seasonings and flavours at 30 ppm, snack foods at 18 ppm, baked goods at 1000 ppm, frozen d airy at 0.7 ppm, meat products at 70.5 ppm, soft candy at 1300 ppm, sweet sauce at 14 ppm, gelatin s and puddings at 520 ppm, non-
alcoholic beverages at 2100 ppm, alcoholic beverages at 0.0066 ppm, hard candy at 53.22 ppm, an d chewing gum at 41 ppm [Fenaroli, 2005].

References - Ingredient Reported Uses

Fenaroli (2005). Fenaroli's Handbook of Flavour Ingredients, 5th Edition. CRC Press, Boca Raton, USA.

TOXICITY DATA

In Vivo Data

Acute Toxicity Data

Mouse LD50 Oral 5105 mg/kg
Rabbit LD50 Skin >20 mL/kg
Rat LD50 Oral 3980 mg/kg
Guinea Pig LD50 Skin >20 mL/kg

In Vivo Carcinogenicity/Mutagenicity

Ethyl acetoacetate is not mutagenic and there is no carcinogenicity data available. Ethyl acetoacetat e is not suspected to be a carcinogen (European Union risk assessment report, 2002).

According to the European Commission risk assessment report, “there is no concern with respect t o mutagenicity” (EC, 2002a)

"Given the lack of indication of mutagenicity and organ toxicity, coupled with an assessment of the chemical structure and metabolic profile, there is no concern for carcinogenicity" (CSTEE, 2002).

According to the European Commission risk assessment report, “from experience on other compar able compounds in combination with the knowledge on the metabolites there is no reason to assum e a concern regarding cancerogenic effects of the substance” (EC, 2002a)

References - In Vivo Carcinogenicity/Mutagenicity

European Union risk assessment report (Ethyl acetoacetate) Vol:13 (2002) p98

EC (2002a). European Commission Joint Research Centre. European Union Summary Risk Assess ment Report. Ethyl acetoacetate CAS No. 141-97-9, EINECS No. 205-516-
1. https://echa.europa.eu/documents/10162/4d3ed256-027b-4286-84d9-bdf67bc32a25

CSTEE (2002). Opinion on the results of the Risk Assessment of: Ethyl acetoacetate - CAS No. 141-97-9, EINECS No. 205-516-1 - report version (human health): Draft of 1 August 2001.

Dermal Toxicity

Ethyl acetoacetate was not irritating when applied at full strength to intact or abraded rabbit skin for 24 h under occlusion. Ethyl acetoacetate was also tested at 8 % in petrolatum and produced no irritation after a 48 h closed-patch test in 26 human subjects. In addition, ethyl acetoactetate produced no sensitisation when tested at a concentration of 8 % in petrolatum in 26 human volunteers [Opdyke, 1974].

The dermal LD50 for rats is > 10000 mg/kg. This value is much higher than the calculated highest dermal exposure of 6 mg/kg (calculated on the basis of 1 mg/cm2, exposed skin area 420 cm2, 70 kg bodyweight). Ethyl acetoacetate is not classified as irritating to skin or eyes or a skin sensitizer. In these studies, no adverse effects were observed after 28 days in the rat at the highest tested oral dose of 1000 mg/kg/day. Comparison of the experimental results of the oral 28-day studies in rats with the highest repeated dermal exposure of 420 mg/day suggests that systemic health risks due to repeated dermal exposure are not expected (European Union Risk Assessment Report, 2002).

There was no evidence of skin irritation when 8% EAA in petrolatum was applied, under 48-hour occlusive cover, to the skin of 26 subjects (Epstein, 1973).

EAA was not irritating when 0.5 ml [about 500 mg] was applied, under semi-occlusive cover, for 4 hours to the skin of albino rabbits in a study performed to OECD guidelines5 (Hoechst AG, 1983a) nor when applied, undiluted, to the intact or abraded skin of rabbits under 24 -hour occluded contact (Moreno, 1973).

No or mild skin irritation was reported in rabbits, depending on the duration of exposure and the dose [no further details available] (Smyth et al., 1949).

Mild skin irritation was reported in an open irritation test in rabbits treated with 510 mg EEA [no further details available] (Union Carbide, 1969).

There was no evidence of skin sensitisation in guinea pigs [no further details available] (Eastman Kodak, 1991).

References - Dermal Toxicity

European Union risk assessment report (Ethyl acetoacetate) Vol:13 (2002) p98

Opdyke (1974). Monographs on Fragrance Raw Materials: Ethyl acetoacetate. Fd. Cosmet. Toxicol., 12, 713.

Hoechst AG (1983a). Acetessigsäureethylester. Prüfung auf akute dermale Reizwirkung/Ätzwirkung am Kaninchen, unpublished report Nr. 83.0409, 1. August 1983 [cited in EC, 2002b; IUCLID, 2000].

Moreno OM (1973). Report to RIFM, 18 May [cited in Opdyke, 1974].

Smyth HF Jr, Carpenter CP and Weil CS (1949). Range-finding toxicity data. List III. Journal of Industrial Hygiene and Toxicology 31, 60-62 [cited in EFSA, 2012; EC, 2002b; HSDB, 2002; RTECS, 2013].

Union Carbide (1969). Union Carbide Data Sheet 3/12/1969 [cited in RTECS, 2013].

Eastman Kodak (1991). Material Safety Data Sheet (12.10.1991) [cited in IUCLID, 2000].

Reproductive/ Developmental Toxicity

From an oral reproductive toxicity screening test a NOAEL of 1000 mg/kg/day was obtained.

Groups of 10 male and 10 female Sprague Dawley/CRL:CD®BR rats were treated, by oral gavage, with 0, 50, 225 and 1000 mg EAA/kg bw/day in tap water from 2 weeks prior to mating until the end of the mating period (males), or until the 4th day of lactation (females), in accordance with OECD guidelines. Parental toxicity (body weights, food consumption, water consumption, pathological examination, behaviour), reproductive organ weights and histopathological examination (testes, epididymides, ovaries), reproductive toxicity (numbers of corpora lutea and implantations, pre-implantation loss, pre-coital time, duration of gestation, parturition), effects on offspring (post-implantation loss, numbers of live pups, sex distribution, frequency of still births and malformations, pup body weights), reproductive indices (birth index, live birth index, viability index) and maternal brood care were noted. Although effects were seen at 1000 mg/kg bw/day and included a slight decrease in the number of corpora lutea and implantations (and hence an increase in pre-implantation loss), corresponding with a slight decrease in the number of pups at birth and at 4 days (and a corresponding increase in post-implantation loss), all values were found to be within the range of historical control data from the same laboratory and were not considered to be treatment-related, by the investigators. The NOAEL was, therefore, 1000 mg/kg bw/day (the highest dose tested) (LPT, 1999, 2000).

References - Reproductive/ Developmental Toxicity

European Union risk assessment report (Ethyl acetoacetate) Vol:13 (2002) p98

LPT (1999). Reproduction/Developmental Toxicity Screening Test of acetoacetic acid ethyl ester by oral administration to Sprague-Dawley rats – OECD Method 421, Report No. 11232/98, June 7, 1999 [cited in EC, 2002b].

LPT (2000). Addendum No. 1 to LPT Report No. 11232/98 [cited in EC, 2002b].

Inhalation Toxicity

The acute inhalation toxicity of ethyl acetoacetate in rats appears to be low. No lethality occurred at saturated vapour conditions with an estimated exposure concentration of 1000 ml/m3 (1 hPa, 20° C). Ethyl acetoacetate is not suspected to be a respiratory tract irritant. In these studies, no adverse effects were observed after 28 days in the rat at the highest tested oral dose of 1000 mg/kg/day. Taking into account a possible chronic threshold level lower than the experimental NOAEL of the subacute rat study, equivalent absorption by the oral and inhalation route, metabolic rate scaling, biotransformation of the carboxylic ester to acetoacetic acid and ethanol, it is assumed that the anticipated human NAEC for chronic inhalation exposure might be between 100 ml/m3 and 1000 ml/m3 (about 500 mg/m3 to 5000 mg/m3) (European Report, 2002).

According to the European Commission risk assessment report, ethyl acetoacetate (EAA) “is not suspected to be a respiratory tract irritant” (EC, 2002a).

According to the European Commission risk assessment report, “inhalation exposure is not suspected to result in respiratory tract sensitization” (EC, 2002a).

According to the European Commission risk assessment report, “during normal use acute inhalation risks are not considered of concern” (EC, 2002a)

The acute inhalation 6-hour LC50 value in rats was reported to be >1129 ppm [>6000 mg/m3] (Eastman Kodak, 1991), while no deaths occurred in rats exposed to “concentrated/saturated vapour” for 8 hours (Smyth et al., 1949).

Based on the 28-day oral toxicity studies in rats and “taking into account a possible chronic threshold level lower than the experimental NOAEL of the subacute rat study, equivalent absorption by the oral and inhalation route, metabolic rate scaling, biotransformation of the carboxylic ester to acetoacetic acid and e

thanol, it is assumed that the anticipated human NAEC10 for chronic inhalation exposure might be between 100 ml/m3 and 1,000 ml/m3 (about 500 mg/m³ to 5,000 mg/m³)" (EC, 2002a).

The size of the mitral cells [olfactory bulb cells of the brain] was altered in newborn rats continuou sly exposed, from day 1 to day 69, to 1-2 ppm EEA [5-
11 mg/m3] when compared with animals exposed to a "normal range of rat colony odors" or deodo rised air (Panhuber and Laing, 1987).

When three Wistar rats were exposed continuously, by inhalation, to 7.8 x 10-
8 M for 4 weeks, degeneration in the olfactory bulb was found (Pinching and Døving, 1974).

References - Inhalation Toxicity

European Union risk assessment report (Ethyl acetoacetate) Vol:13 (2002) p98

EC (2002a). European Commission Joint Research Centre. European Union Summary Risk Assess ment Report. Ethyl acetoacetate CAS No. 141-97-9, EINECS No. 205-516-
1. https://echa.europa.eu/documents/10162/4d3ed256-027b-4286-84d9-bdf67bc32a25

Eastman Kodak (1991). Material Safety Data Sheet (12.10.1991) [cited in IUCLID, 2000].

Smyth HF Jr, Carpenter CP and Weil CS (1949). Range-
finding toxicity data. List III. Journal of Industrial Hygiene and Toxicology 31, 60-
62 [cited in EFSA, 2012; EC, 2002b; HSDB, 2002; RTECS, 2013].

Panhuber H and Laing DG (1987). The size of mitral cells is altered when rats are exposed to an od or from their day of birth. Developmental Brain Research 34, 133-140.

Pinching AJ and Døving KB (1974). Selective degeneration in the rat olfactory bulb following exp osure to different odours. Brain Research 82, 195-204 [cited in IUCLID, 2000].

Cardiac Toxicity

Decreases in blood pressure and pulmonary arterial blood flow, which were accompanied by a slig ht fall or no change, followed by a rise in pulmonary arterial pressure, were seen in 8 anaesthetized cats injected, intravenously, with 100-
200 mg EAA. Arrest of respiration, sometimes rapid, shallow breathing and, occasionally, a diminu tion in tidal air were also noted, these effects being shown to be a reflex due to receptors in the lun g (Barer and Nüsser, 1958).

There were no effects on organ weights or macroscopic and microscopic examination [of unspecifi ed organs and tissues but may have included the heart and lung] when groups of 5 male and 5 fema le Sprague-
Dawley rats were treated, by oral gavage, with up to 1000 mg/kg bw/day [presumably daily] for 4 consecutive weeks, in accordance with OECD guidelines (Hazleton, 1991).

References - Cardiac Toxicity

Barer GR and Nüsser E (1958). Cardiac output during excitation of chemoreflexes in the cat. Britis h Journal of Pharmacology Chemotherapy13, 372-377.

Hazleton (1991). Study-No. 733/502, Rep.-
No. 790, im Auftrag von Lonza AG (HOE 91.0638). 4 week oral (gavage) toxicity study in the rat f ollowed by a 2-week treatment-free period [cited in EC, 2002b].

Addictive Data

No Data Identified

References - Addictive Data

No Data Identified

Behavioral data

No Data Identified

References - Behavioral data

No Data Identified

In Vivo - Other Relevant Studies

Ethyl acetoacetate encapsulated in gum arabic was administered in rodent diet for a minimum of 2 8 consecutive days to groups of 16 male and 16 female rats (Sprague-
Dawley strain) at levels of approximately 100, 300 and 1000 mg/kg body weight/day. The administ ration of ethyl acetoacetate in the diet did not adversely affect the growth or general health of the a nimals or their food intakes. None of the minor variations observed in the haematology, serum che mical analyses or urine analyses are considered to be indicative of a treatment-
related toxic effect. Caecal enlargement was seen in male rats treated with the top dose of ethyl ace toacetate, but this was accompanied by a normal histopathology. Few histopathological abnormaliti es were observed. Proteinaceous casts were found in the bladder of approximately half the male rat s given 1000 mg ethyl acetoacetate/kg, and nephrocalcinosis was a common occurrence in female r ats in this dose group. Renal function was unimpaired in treated male and female rats, and the histo pathological findings are common in the strain of rats chosen for this study. Although the caecal en largement and the changes in kidney and bladder of rats given 1000 mg ethyl acetoacetate/kg are n oted, it is considered that ethyl acetoacetate did not produce treatment-
related adverse effects in rats during this study [Cook et al., 1992).

Preliminary studies have shown that acetoacetic acid ethyl ester is metabolized to acetone in anima ls.
http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~FOBo9C:54

Moderate (Marhold, 1986) and severe (Carpenter and Smyth, 1946) eye irritation occurred in stand ard Draize tests in rabbits treated with 100 mg. Two further studies in rabbits reported mild eye irrit ation [no further details available] (Smyth et al., 1949) and slight irritation in a Draize test, conduct ed according to OECD guidelines and using 0.1 ml EAA [about 100 mg] (not irritating according t o EU classification). In the latter test, there was no effect on the cornea, moderate irritation of the c onjunctiva (which was reversible within 2 days) and slight iridial redness in 1/3 animals (which wa s reversible within 3 days) (Hoechst AG, 1983b).

Groups of 16 male and 16 female Sprague-
Dawley rats were given oral doses of 0, 100, 300 or 1000 mg EAA/kg bw/day encapsulated in gum Arabic for 28-
29 days. Although there were some haematological changes and caecal enlargement and bladder ch anges (proteinaceous casts) were noted in the males and kidney changes (nephrocalcinosis) were se en in the females treated with 1000 mg/kg bw/day, the effects were not considered to be of toxicolo gical significance by the investigators. The NOAEL was, therefore, 1000 mg/kg bw/day (the highe st dose tested) (Cook et al., 1992). [According to EFSA (2012) the NOAEL is 300 mg/kg bw/day.]

Groups of 5 male and 5 female Sprague-
Dawley rats were treated, by oral gavage, with 0, 50, 225 or 1000 mg/kg bw/day [presumably daily] for 4 consecutive weeks, in accordance with OECD guidelines. There were no deaths and no effe cts on body weight gain, food consumption, eye lesions, haematology, clinical chemistry, organ we ights or macroscopic and microscopic examination. Salivation was seen at 1000 mg/kg bw/day but the NOAEL was determined to be 1000 mg/kg bw/day (the highest dose tested) (Hazleton, 1991).

References - In Vivo - Other Relevant Studies

Cook WM, Purchase R, Ford GP, Creasy DM, Brantom PG, Gangolli SD (1992). A 28-
day feeding study with ethyl acetoacetate in rats. Food. Chem. Toxicol. 30(7):567-73.

Marhold J (1986). Prehled Prumyslove Toxikologie; Organicke Latky, 729. Prague, Czechoslovaki a, Avicenum [cited in RTECS, 2013].

Carpenter CP and Smyth HF Jr (1946). Chemical burns of the rabbit cornea. American Journal of Ophthalmology 29, 1363-1372 [cited in RTECS, 2013].

Smyth HF Jr, Carpenter CP and Weil CS (1949). Range-finding toxicity data. List III. Journal of Industrial Hygiene and Toxicology 31, 60-62 [cited in EFSA, 2012; EC, 2002b; HSDB, 2002; RTECS, 2013].

Hoechst AG (1983b). Acetessigsäureethylester. Prüfung auf akute Reizwirkung/Ätzwirkung am Auge beim Kaninchen, unpublished report Nr. 83.0410, 1. August 1983 [cited in EC, 2002b; IUCLID, 2000].

Cook WM, Purchase R, Ford GP, Creasy DM, Brantom PG and Gangolli SD (1992). A 28-day feeding study with ethyl acetoacetate in rats. Food and Chemical Toxicology 30, 567-573.

EFSA (2012). European Food Safety Authority. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Scientific Opinion on Flavouring Group Evaluation 10, Revision 3 (FGE.10Rev3): Aliphatic primary and secondary saturated and unsaturated alcohols, aldehydes, acetals, carboxylic acids and esters containing an additional oxygenated functional group and lactones from chemical groups 9, 13 and 30. EFSA Journal 10(3), 2563. http://www.efsa.europa.eu/en/efsajournal/doc/2563.pdf

Hazleton (1991). Study-No. 733/502, Rep.-No. 790, im Auftrag von Lonza AG (HOE 91.0638). 4 week oral (gavage) toxicity study in the rat followed by a 2-week treatment-free period [cited in EC, 2002b].

In Vitro Data

In Vitro Carcinogenicity/Mutagenicity

Mutagenicity of ethyl acetoacetate was negative in Salmonella strains TA97, TA98, TA100, TA1535 and TA1537 at up to 10 mg/plate ± metabolic activation and in E.Coli strain WP2UVRA at up to 5000 µg/plate ± metabolic activation [HSDB, 1996].

In chromosome aberration tests, there was no evidence of chromosome damage in Chinese hamster fibroblast (CHL) cells treated with up to 2 mg/ml (Ishidate et al., 1984) or in Chinese hamster lung (V79) cells treated with up to 1.3 mg/ml (a cytotoxic concentration) (Hoechst Marion Roussel, 1999), both with and without S9 and evaluated after 48 and 20 hours respectively.

There was no evidence of mutagenicity in bacterial reverse mutation (Ames) assays in which Salmonella typhimurium strains TA92, TA94, TA98, TA100, TA1535 and TA1537 were treated with up to 25 mg/plate (Ishidate et al., 1984), S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 and Escherichia coli strain WP2 uvrA were treated with up to 10 mg/plate (Hoechst AG, 1988) and S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 and E. coli strain WP2 uvrA were treated with up to 5 mg/plate (JETOC, 1996), all conducted with and without S9. Further negative results were obtained in S. typhimurium strains TA97 and TA102 treated, with and without S9, with 0.1-10 mg/plate (Fujita and Sasaki, 1987) and in unspecified S. typhimurium strains treated with up to 25 mg/plate [no further details available] (Anon., 1982).

In a Japanese study, positive mutagenicity was seen in E. coli WP2 uvrA treated with 0.2-1.6 mg/plate [probably] without S9 [no further details available from the English tables] (Yoo, 1986).

DNA damage was seen in a recombination-repair (Rec)-assay in which Bacillus subtilis strains H17 and M45 were treated with 20 µl/disk (20 mg/disk) [no further details available from the English tables] (Yoo, 1986). A further Rec-assay, conducted with and without S9 in B. subtilis strains H17 and M45 at 10-20 µl/ml (10-20 mg/ml) was both negative and positive according to EFSA (2012; only the abstract was apparen

tly translated) and weakly positive according to JECFA (2000) (Kuroda et al., 1984). There was no test (no inhibition in either strain) when B. subtilis strains H17 and M45 were treated with 0.02 mg /disk in a Rec-
assay, with and without S9 [paper in Japanese, no further details available from the English tables] (Oda et al., 1978)

References - In Vitro Carcinogenicity/Mutagenicity

HSDB, 1996. Hazardous Substances Data Bank - Toxnet - National Institutes of Health

Ishidate M, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M and Matsuoka A (1984). Pri mary mutagenicity screening of food additives currently used in Japan. Food and Chemical Toxicol ogy 22, 623-636.

Hoechst Marion Roussel (1999). Acetoacetic acid ethyl ester. In vitro mammalian chromosome abe rration test in V79 Chinese hamster cells (Report No. 99.0162), unpublished [cited in EC, 2002b].

Hoechst AG (1988). Acetessigsäureethylester, study of the mutagenic potential in strains of Salmon ella typhimurium (Ames test) and Escherichia coli. Unpublished report Nr 88.0512, 1988 [cited in EC, 2002b].

JETOC (1996). Japan Chemical Industry Ecology-
Toxicology & Information Center. Mutagenicity test data of existing chemical substances based on the toxicity investigation system of the Industrial Safety and Health Law. Ethyl acetoacetate, p165.

Fujita H and Sasaki M (1987). Mutagenicity test of food additives with Salmonella typhimurium T A97 and TA102 (in Japanese). Annual Report of Tokyo Metropolitan Research Laboratory of Publi c Health 38, 423-430 [cited in EFSA, 2012].

Anon. (1982). [Japanese reference, not translated] 5, 579-587 [cited in Yoo, 1986].

Yoo YS (1986). Mutagenic and antimutagenic activities of flavouring agents used in foodstuffs. Jo urnal of the Osaka City Medical Center 34, 267-288.

EFSA (2012). European Food Safety Authority. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Scientific Opinion on Flavouring Group Evaluation 10, R evision 3 (FGE.10Rev3): Aliphatic primary and secondary saturated and unsaturated alcohols, alde hydes, acetals, carboxylic acids and esters containing an additional oxygenated functional group an d lactones from chemical groups 9, 13 and 30. EFSA Journal 10(3), 2563. http://www.efsa.europa.e u/en/efsajournal/doc/2563.pdf

JECFA (2000). Safety evaluation of certain food additives and contaminants. Aliphatic primary alc ohols, aldehydes, carboxylic acids, acetals, and esters containing additional oxygenated functional groups. Prepared by the fifty-
third meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series 44. World Health Organization, Geneva. http://www.inchem.org/documents/jecfa/jecmono/v 44jec10.htm

Kuroda K, Tanaka S, Yu YS and Ishibashi T (1984). Rec-
assay of food additives. Nippon Koshu Eisei Zasshi 31, 277-
281 [cited in EFSA, 2012; JECFA, 2000].

Oda Y, Hamono Y, Inoue K, Yamamoto H, Niihara T and Kunita N (1978). Mutagenicity of food fl avours in bacteria (1st report). Osaka-Furitsu Koshu Eisei Kekyu Shokuhin Eisei Hen 9, 177-
181 (in Japanese, tables in English).

In Vitro - Other Relevant Studies

No Data Identified

References - In Vitro - Other Relevant Studies

No Data Identified

Emissions and Associated Toxicity Data

A recent mouse skin painting study investigated the carcinogenicity of condensate prepared from ci garettes containing a number of additives in combination, including ethyl acetoacetate at 1 ppm. T he authors concluded that the study "did not indicate any substantive effect of these ingredients on the tumorigenicity of cigarette smoke condensate" [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)] [Gaworski et al., 1999].

The addition of ethyl acetoacetate 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 addi tion of ethyl acetoacetate to a reference cigarette had no discernable effect upon the type or severit y of the treatment related pathological changes associated with tobacco smoke exposure [Baker et a l., 2004].

When tested at 1 ppm in cigarettes, in a 13-week inhalation study, the presence of ethyl acetoacetate had no discernible effect on the character of extent of the biologic responses normally associated with inhalation of mainstream cigarette sm oke in rats" [Gaworski et al., 1998] [however, it should be noted that the cigarettes had been spike d with a number of flavour ingredients in combination prior to smoking, and they contained a typic al 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].

Baker et al., [2004], examined the effects of the addition of 482 tobacco ingredients upon the biolo gical 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 acetoacetate at 12 ppm was determined not to have affected the mutagenicity of the total p articulate 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]

References - Emissions and Associated Toxicity Data

Gaworski et al., (1999). Toxicologic evaluation of flavor ingredients added to cigarette tobacco: ski n painting bioassay of cigarette smoke condensate in SENCAR mice. Toxicology, 139, 1-17.

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

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.