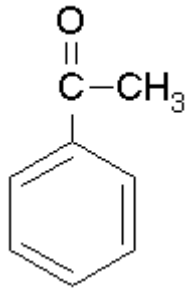
ACETOPHENONE

SYNONYMS

Acetyl benzene
Acetyl benzol
Benzoyl methide
Methyl phenyl ketone
Phenyl methyl ketone
2-Acetopyridine

CHEMICAL STRUCTURE



CHEMICAL FORMULA

C_8H_8O

IDENTIFIER DETAILS

CAS Number	:	98-86-2
CoE Number	:	138
FEMA	:	2009
EINECS Number	:	202-708-7
E Number	:	-

SPECIFICATIONS

Melting Point: 20.5 C [Sigma-Aldrich, 2002].

Boiling point: 201.7 C [Sigma-Aldrich, 2002].

PURPOSE

Flavouring substance

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
1	10	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
ACCEPTABLE	JECFA	2001	No safety concern at current levels of usage when used as a flavouring agent

FDA Status: [CFR21]

Section Number	Comments
172.515	Synthetic flavouring substances and adjuvants

HUMAN EXPOSURE

Natural Occurrence: Acetophenone has been reported found in the oils of labdanum, *Stirlingia latifolia, Urtica dioi ca, Elsholtzia argyi* var. *nipponica, Elsholtzia ciliata,* in various species of *Orthodon* [O. *citralferum,* O. *linalooliferum* var. *laerolinalooliferum,* O. *linaloiferum,* O. *sabinoliferum* var. *taiwanense*], and in castoreum absolute [Fenaroli, 2005].

Reported Uses: Acetophenone is reportedl y used in frozen dairy at 14.45 ppm, soft candy at 28.25 ppm, gelatin pudding at 24.50 ppm, non-alcoholic beverages at 5.93 ppm, alcoholic beverages at 1 ppm, hard candy at 28.3 ppm, and chewing gum at 45.07 ppm, [Fenaroli, 2005]. Cranberry 0.02-0.1 mg/kg, other fruits up to 0.01 mg/kg, b eans 0.02 mg/kg, cocoa, 1.5-2.6 mg/kg [CoE, 2002].

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 acetophenone at 1.3 ppm, were compared to a typical commercial tobacco blend without flavouring ingre dients. 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 refere nce 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 recov ery 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 betw een smoke from cigarettes containing the flavouring or casing ingredients and reference cigarettes.

TOXICITY DATA

This ingredient has been registered under REACH. Under REACH, registrants have an obligation to provide information on substances they manuf acture 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/.

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 33 3 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], determin ation 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 acetophenone at levels up to 4 ppm, "did not increase the overall toxicity of cigarette smoke"

In Vivo Toxicity Status

Species	Test Type	Route	Reported Dosage
Rat	LD_{50}	Oral	815 mg/kg/bw
Mouse	LD_{50}	Oral	740 mg/kg/bw
Mouse	LD_{50}	Intraperitoneal	200 mg/kg/bw
Mouse	LDL_0	Subcutaneous	330 mg/kg/bw
Rabbit	LDL_0	Dermal	15900 L/kg/bw
Guinea pig	LDL_0	Dermal	>20 ml/kg bw
Mouse	LC_{50}	Inhalation	>210 ppm (8hr exposure) [RTECS, 2002]
Rabbit	Irritation	Dermal	515mg Mild irritant
Rabbit	Irritation	Ocular	750 g Severe irritant, [This dose produced severe corneal necrosis Lewis, 2002]

The intraperitoneal [i.p] injection of 0.4-0.5g/kg acetophenone to rats [unspecified strain] leads to the paralysis of all limbs 20 minutes after injection, convulsions were also observed in Guinea-pigs. However , a deep sleep and eventual respiratory arrhythmia was observed in dogs, [the original text is unclear and doses in guinea-pig and dogs not clearly stated], [HSDB, 2002].

Acetophenone is thought to be readily absorbed percutaneously in mice whose tails w ere immersed into acetophenone, all died within a 4 hr period [HSDB, 2002].

Six rats of an unspecified strain survived an 8 hr exposure to a saturated atmosphere of acetophenone. The maximum vapour concentration at 20 ^{o}C

was 430ppm which was reported to be equivalent to 2130 mg/m ^{3}, [BIBRA, 2002].

Groups of 5 male and 5 female weanling Osborne Mendel rats received acetophenone in the diet at concentrations of 0, 1000, 2500 and 10,000 ppm for 17 weeks (Corresponding to 100, 250 and 1000 mg/kg/day). Histopathological evaluation of the heart, liver, kidneys, spleen, and testis showed no treatment related effects. The NOAEL was reported to be 1000 mg/kg [Hagan *et al.,* 1967]. U.S. EPA health scientists from several Program Offices and the Office of Research and Development assessed acetophenone and derived an oral RfD of 0.1 mg/kg bw/day (last revised 1989) using the NOAEL derived from Hagan et al., (1967). Uncertainty factors applied were 10 for species to species extrapolation, 10 to protect sensitive humans, 10 to extrapolate from subchronic to chronic exposure, and 3 for the lack of important reproductive toxicity data [IRIS, 1989].

Six rats [no strain given] fed 102 mg/kg/day acetophenone for 30 days were not reported to show 'effects' [no specific effects specified] and none of the six animals were reported to die, [ACGIH, 2001].

Carcinogenicity and Mutagenicity

Similarly, a recent mouse skin painting study investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including acetophenone 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)] [Gaworski *et al.*, 1999].

Dermal Toxicity

Although observed to be a skin and eye irritant [depending on length of contact] the vapours from acetophenone are not expected to be a hazard unless it is heated, [HSDB, 2002].

Reproductive and Developmental Toxicity

The application of 0.48 g/kg acetophenone to the skin of pregnant rats [days 10-15 of pregnancy] did not alter the gestation period, size of litter, time of appearance of hair and teeth, opening of eyes or the appearance of reflexes, [no other details were given] [HSDB, 2002].

Acetophenone was administered to groups of 10 male and female Sprague-Dawley rats at 0, 75, 225 and 750 mg/kg/day for 28 days by oral gavage. There was no mortality in the toxicity study. The males from the study were then bred with new females (10 per group) which were dosed at 0, 75, 225 and 750 mg/kg/day between days 3-17 of lactation. 75 mg/kg was determined

to be the NOAEL for the systemic toxicity study, 225 mg/kg/day was determined to be the NOAEL for the neurological aspects of the study. The live birth index, pup survival and mean pup weight during the lactation phase of the reproductive study were decreased during the lactating phase of the study, with the NOAEL of the reproductive study being determined as 225 mg/kg/day [Kapp *et al.,* 2003].

Inhalation Toxicity

Two-week-old rats exposed to acetophenone for 1 - 12 weeks showed specific patterns of mitral cell degeneration in the olfactory bulb, [HSDB, 2002].

Zissu, (1995) reported that 111.0 11.6 ppm acetophenone was observed to have no effect on the histopathology of the respiratory tract, [lesion intensity in the nasal passages] of Swiss mice exposed for 4, 9 or 14 days [Zissu, 1995].

A recent study investigated the effect of cigarettes, containing various additives in three combinations, in a 90-day nose-only smoke inhalati on study in rats. These ingredients included acetophenone at 4 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 ad dition 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 acetophenone at 53 ppm to ref erence 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 acetophenone to a reference cigarette had no discernable ef fect upon the type or severity of the treatment related pathological changes associated with tobacco smoke exposure [Baker *et al.,* 2004]

When tested at 0.8 ppm in cigarettes, in a 13-week inhalation study, the presence of acetophenone 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] [h owever, it should be noted that the cigarettes had been spiked with a number of flavour ingred ients 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].

Other relevant studies

Acetophenone has been listed as a hazardous air pollutant, which could potentially cause serious health problems. In 2001 a Threshold Limit Value Time-weighted average of 10 ppm [49 mg/m ^{3}] was recommended for occupational exposure, [HSDB, 2002]. This value is reported to minimize eye

irritation and ocular sensitivity to light which has been reported at 0.01 mg/m^3, which has been based on a 24 hr/day exposure [ACGIH, 2001].

Human subjects who had ingested 0.1 - 0.3 g acetophenone did not report any signs of toxicity. However, when the dosage was increased to 0.45 - 0.6 g the pulse was observed to weaken which was accompanied by a decrease in haemoglobin, and an increase in micturition. The reduced haemoglobin was reversed when the intake of acetophenone was stopped [no further details were given] [HSDB, 2002].

Alpha and -unsaturated ketones have been reported to be liberated from Mannich bases by the deamination process *in vivo* or under simulated conditions *in vitro* and have been shown to have anti-tumour and cytotoxic effects, [Gul *et al*., 2000]. Gul *et al*., (2000) also reported that the Mannich bases derived from acetophenone within their studies were cytotoxic in both mouse renal carcinoma and human T-cell lines and therefore may have a potential clinical application [Gul *et al*., 2000].

Acetophenone has been shown to be rapidly absorbed from the gut and, metabolised in the liver and excreted predominantly in the urine and only to a very small extent in the faeces. Approximately half of a dose of 480 mg/kg/bw administered to rabbits was detected in the urine after 24 hours [JECFA 2002].

Behavioural Data

Acetophenone has been used as a hypnotic agent and has been reported to be converted to benzoic acid and methylphenylcarbinol in dogs and rabbits. Small amounts have been reported to be excreted as mandelic acid [2 %] . In rabbit half of an administered acetophenone dose is excreted as methylphenylcarbinyl glucuronide and 20 % as hippuric acid, [Opdyke, 1973].

Acetophenone is reported to have no effect on hexobarbital-induced sleeping time, urinary ascorbic acid excretion, or hepatic microsomal amidopyrine- *N*-demethylation, [ACGIH, 2001].

Acetophenone has been shown to have a sedative effect. At high doses it has also been observed to have a depressant action on the pulse rate and a decrease in the level of human haemoglobin [HSDB, 2002].

***In Vitro* Toxicity Status**

Carcinogenicity and Mutagenicity

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 added ingredients, which included acetophenone at levels up to 10,000 ppm 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 tob acco [Gaworski *et al*., 2011].

Assay	**Strain**	**Results**
Rec-assay, DNA effects [Bacterial DNA repair]	*Escherichia coli* polA [W3110 vs p3478]	Negative
Rec-assay, DNA effects [Bacterial DNA repair]	*Escherichia coli* polA [W3119 vs p3478]	Negative

[Above data obtained from GENE-TOX, 2002- no doses were given]

AMES Pre-incubation [Rat S9]	*Salmonella typhimurium* [TA97, TA102]	Negative 0.1-1mg/plate [CCRIS, 2002]
	[TA 98, TA100, TA2637]	Negative 50-1000 mg/plate [JECFA 2002]
	[TA1535, TA100, C3076, TA1537, D3052, TA1538 and TA98]	Negative 1-1000mg/ml [JECFA 2002]
Rec-assay, [DNA effects]	*Bacillus subtilis* [H17 and M45]	Negative [Oda *et al*., 1978]

Acetophenone [FL-no: 07.004] was negati ve in the Ames assay in various *Salmonella typhimurium* strains tested in several different studies (TA 97, TA98, TA 100, TA 102, TA1535, TA 1537, TA 1538, TA 2637, C3076, D3052, G45, *E.Coli* WP2 and *E.Coli* WP2uvrA) induced chromosomal aberrations *in vitro* in the presence of metabolic activation [EFSA, 2008].

In several strains of *Salmonella typhimurium* [not specified] acetophenone on application at levels up to 3000 nmol/plate did not have any reverse mutation activity in the absence and presence of rat S-9, [BIBRA, 1991].

Acetophenone was observed to cause DNA strand breaks in *E.coli* [B(3)T-] after strand photosensitisation, [dose not stated] [IRIS, 2002]. Acetophenone is known to cause photosensitive thymine dimerisation of DNA,being used as a positive control for thymine dimerisation experiments [Chouni-Lalanne et al., 1998].

Rahn *et al* ., (1974) reported on the chain breaking that occurs with acetophenone on photosensitised DNA [isolated from *Escherichia coli* B(3)T^-], [at 313nm], [Rahn *et al*., 1974].

Acetophenone produced chromosomal damage in hamster lung cells [600mg/L] in the presence of metabolic activation however, in the absence of S-9 no effect was observed, [RTECS, 2002; BIBRA, 1991].

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 upt ake 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 acetophenone at levels up to 4 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 acetophenone at 53 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 condens ate 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 cigare tte smoke was not increased by the addition of the ingredients, which included acetophenone at levels up to 134 ppm[In vitro toxicity testing of tobacco ingredients in burnt form (Internal document R-53)]

PYROLYSIS AND TRANSFER STUDIES

Information relating to the pyrolysis and/or transfer of acetophenone 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 cond itions 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.

A 2004 study by Baker and Bishop analysed the pyrolytic breakdown of 291 tobacco ingredients using combustion conditions that simulate cigarette combustion. Due to the combustion conditions the results likely predict the natural behavio ur of these compounds during combustion on the cigarette, and allow estimation of the degree of intact transfer into the mainstream smoke. Under pyrolysis acetophenone was found to transfer 99.8% intact. The only breakdown product was benzoic acid (0.2%).

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