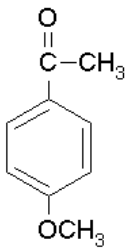
Acetanisole

Ingredient synonym names

4'-Methoxyacetophenone;
Acetophenone;
4'-methoxy- Ethanone, 1-(4-methoxyphenyl)- ;
p-Acetylanisole;
4-Acetylanisole;
4-Methoxy acetophenone;
Methyl-4-methoxy phenyl ketone;
Ethanone, 1-(4-methoxy phenol);
Anisyl, p-methyl ketone;
para-Acetylanisole;
para-Methoxyphenyl methyl ketone;
para-Methoxyacetophenone;
Linarodin;
Novatone;
Vananote;

IDENTIFIER DETAILS

Ingredient chemical structure



CAS Number	FEMA Number	Additive Number	Ingredient EC Number
100-06-1	2005	-	202-815-9

CAS Additional Number	FL Number	CoE Number
-	07.038	570

Chemical formula C9H10O2

Ingredient CLP Classification

Ingredient REACH Registration Number

01-2119929048-35

Acute Oral Toxicity	Eye Damage/Irritation	Carcinogenity
4	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

Acetanisole

0	0	0

SPECIFICATIONS

Melting Point	37-40 degrees C	Boiling Point	152-154 degrees C

STATUS IN FOOD AND DRUG LAWS

Acceptable Daily Intake (ADI, mg/kg)	Acceptable (JECFA 2001)
Acceptable Daily Intake (ADI) comments	No safety concern at current levels of intake when used as a flavouring agent.
FDA Status	21 CFR 172.515: Synthetic flavouring substances and adjuvants

CoE limits - Beverages (mg/kg)	10	CoE limits - Food (mg/kg)	20	CoE limits - Exceptions (mg/kg)	-

HUMAN EXPOSURE

Ingredient Natural Occurence (if applicable)

Acetanisole is reportedly found in anise seed, cranberry, black coke berry, grape, heated beef and sherry [Fenaroli 2005; CoE, 2000].

References - Ingredient Natural Occurence

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

Fenaroli (2005) Fenaroli's handbook of flavour ingredients, Volume II 5th Edition CRC press.

Ingredient Reported Uses

Acetanisole is reportedly used in baked goods at 1.5 ppm, frozen dairy at 1.0 ppm, meat products at 100 ppm, soft candy at 7.1 ppm, gelatin pudding at 0.2 ppm, non-alcoholic beverages at 7.8 ppm, alcoholic beverages at 0.0001 ppm, hard candy at 278.3 ppm, and chewing gum at 110 ppm [Fenaroli, 2005]. The estimated per capita intake of acetanisole was calculated to be in Europe 150 □g/day and 84 □g/day per person in the USA [JECFA, 2002]

References - Ingredient Reported Uses

Fenaroli (2005) Fenaroli's handbook of flavour ingredients, Volume II 5th Edition CRC press.

JECFA (2001) Safety evaluation of certain food additives and contaminants. Prepared by the Fifty-fifth meeting of the joint FAO/WHO Expert Committee on Food Additives (JECFA). ICPCS Geneva.

Acetanisole

TOXICITY DATA

In Vivo Data

Acute Toxicity Data

LD50 1720 mg/kg - rat (oral) [JECFA 2002]
LD50 820 mg/kg – mouse (oral) [Lewis 2000]
LD50 >5000mg/kg - rabbit (skin) [RTECS]

Moderate 500 mg/24 hr - rabbit (skin) [Lewis 2000]

TCLo 1700 ug/m3 39W - human (inhalation) [RTECS]
TCLo 152 mg/m3/4hr/13w - rat (inhalation) [RTECS]

JECFA (2002) Safety evaluation of certain food additives and contaminants. Prepared by the fifty-seventh meeting of the joint FAO/WHO Expert Committee on Food Additives (JECFA). ICPCS Geneva

Lewis (2000) Sax's Dangerous Properties of Industrial Materials. Vol 3. John Wiley & Sons Inc New York. pp2337.

RTECS [Registry of Toxic Effects of Chemical Substances). Search carried out on 09/07/02. RTECS No. AM9240000.

In Vivo Carcinogenicity/Mutagenicity

When considering a group of 33 aromatic substituted secondary alcohols, ketones and related esters, including 4'-methylacetophenone, the EFSA AFC Panel felt that "the limited data available do not allow a final assessment of genotoxicity. From the data available there is some indication of genotoxic potential for two of the supporting substances (1-phenylethan-1-ol and acetophenone). However, in the light that 1-phenylethan-1-ol can be metabolised to acetophenone and vice versa and that the results of acarcinogenicity study with 1-phenylethan-1-ol in mice and rats do not give rise to concern, the Panel concluded that the positive in vitro results for the two supporting substances do not give rise to concern with respect to carcinogenicity in humans (EFSA, 2008).

A structure-activity relationship model used to predict the carcinogenic potential of acetanisole predicted no carcinogenic effect in rodents (Rosenkranz et al., 1998).

References - In Vivo Carcinogenicity/Mutagenicity

EFSA (2008). European Food Safety Authority. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food. Flavouring Group Evaluation 69, (FGE.69): Consideration of aromatic substituted secondary alcohols, ketones and related esters evaluated by JECFA (57th meeting) structurally related to aromatic ketones from chemical group 21 evaluated by EFSA in FGE.16 (2006). EFSA Journal 869, 1-35.

Rosenkranz HS, Zhang YP and Klopman G (1998). Studies on the potential for genotoxic carcinogenicity of fragrances and other chemicals. Food and Chemical Toxicology 36, 687-696.

Dermal Toxicity

When tested at a concentration of 6% in petrolatum, acetanisole was reported not to produce irritation after 48 hours with an occluded patch test in human volunteers. Acetanisole when test at 6% in petrolatum was reported to cause no sensitisation reactions when tested in 25 human volunteers following a maximisation procedure [Opdyke, 1974].

To evaluate chems. (e.g., lipophilic chems., pre/pro-haptens) that are difficult to correctly evaluate using in vitro skin sensitization tests (e.g., DPRA, KeratinoSens or h-CLAT), the authors developed a novel in vitro test termed "Epidermal Sensitization Assay: EpiSensA" that uses reconstructed human epidermis. This assay is based on the induction of multiple marker genes (ATF3, IL-8, DNAJB4 and GCLM) related to two keratinocyte responses (inflammatory or cytoprotective) in the induction of skin sensitization. Here, the authors first confirmed the mechanistic relevance of these marker genes by focusing on key mols. that regulate keratinocyte responses in vivo (P2X7 for inflammatory and Nrf2 for cytoprotective responses). The up-regulation of ATF3 and IL-8, or DNAJB4 and GCLM induced by the representative sensitizer 2,4-dinitrochlorobenzene in human keratinocytes was significantly suppressed by a P2X7 specific antagonist KN-62, or by Nrf2 siRNA, resp., which supported mechanistic relevance of marker genes. Moreover, the EpiSensA had sensitivity, specificity and accuracy of 93%, 100% and 93% for 29 lipophilic chems. (logKow â‰¥3.5), and of 96%, 75% and 88% for 43 hydrophilic chems. including 11 pre/pro-haptens, compared with the LLNA. These results suggested that the EpiSensA could be a mechanism-based test applicable to broad sets of chems. including lipophilic chems. and pre/pro-haptens. (Saito et al, 2017).

References - Dermal Toxicity

Opdyke (1974) Monographs on fragrance raw materials: acetanisole. Fd Cosmet Toxicol. 12: 927-930.

Saito, Kazutoshi Takenouchi, Osamu Nukada, Yuko Miyazawa, Masaaki Sakaguchi, Hitoshi, An in vitro skin sensitization assay termed EpiSensA for braod sets of chemicals including lipophilic chemicals and pre/pro-haptens, Toxicol. In Vitro volume: 40 pages:

Reproductive/ Developmental Toxicity

No data idenitified

References - Reproductive/ Developmental Toxicity

No data idenitified

Inhalation Toxicity

Exposure of animals to acetylanisole showed slight toxic effects of the substance. It is absorbed by the skin and inhibits central nervous system activity. Medical examination of workers engaged in drying and packing of acetylanisole revealed cardiovascular function changes including increases of dynamic blood pressure and pulse rate, and a pronounced increase of the sense of smell, which demonstrates the strong olfactory inhibition properties of acetylanisole. A tentative safe exposure level for acetylanisole of 3mg/m|3| is proposed. It falls in hazard class III.

References - Inhalation Toxicity

Makaruk et al., (1985) Toxicological assessment of acetylanisole. Giginea I santtarija. 4: 86-87.

Cardiac Toxicity

An increase in pulse rate and blood pressure was noted in humans following “intermittent” inhalation exposure for 39 weeks to 1.7 mg/m3 (Makaruk and Vaganova, 1985).

References - Cardiac Toxicity

Makaruk MI and Vagonova LV (1985). Toxicological characteristics of acetylanisole. Gigiena I Sanitariya 50, 86-87 [in Russian, cited in RTECS, 2015; SCENIHR, 2016].

Addictive Data

No data idenitified

References - Addictive Data

No data idenitified

Behavioral data

No data identified

References - Behavioral data

No data identified

In Vivo - Other Relevant Studies

No data identified

References - In Vivo - Other Relevant Studies

No data identified

In Vitro Data

In Vitro Carcinogenicity/Mutagenicity

When considering a group of 33 aromatic substituted secondary alcohols, ketones and related esters, including 4'-methylacetophenone, the EFSA AFC Panel felt that "the limited data available do not allow a final assessment of genotoxicity.Regarding the prediction of risk of heritable mutations to man, adequate data on germ cell mutagenicity were not available nor data from a two-generation developmental toxicity study. However, toxicokinetic data on another structurally related substance (4-phenyl-3-buten-2-one) indicate that orally administered phenyl alkyl ketones undergo essentially complete first-pass metabolism prior to systemic distribution and that germ cells are unlikely to be exposed. Therefore, the Panel concluded that the positive in vitro results for the two supporting substances do not give rise to concern with respect to heritable mutations in humans" (EFSA, 2008).

References - In Vitro Carcinogenicity/Mutagenicity

EFSA (2008). European Food Safety Authority. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food. Flavouring Group Evaluation 69, (FGE.69): Consideration of aromatic substituted secondary alcohols, ketones and related esters evaluated by JECFA (57th meeting) structurally related to aromatic ketones from chemical group 21 evaluated by EFSA in FGE.16 (2006). EFSA Journal 869, 1-35.

In Vitro - Other Relevant Studies

In vitro incubation of acetanisole with an aromatic ketone reductase from the rabbit kidney resulted in the reduction of the substrate to 1[p-methoxyphenyl] ethanol. The reaction was reported to be reversible depending upon the reaction conditions [Culp et al., 1968].

References - In Vitro - Other Relevant Studies

Culp et al., (1968) Jour Biol Chem 243: 848-852.

Emissions and Associated Toxicity Data

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 acetanisole at levels up to 3 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

The addition of acetanisole 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 acetanisole 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].

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 acetanisole 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].

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 acetanisole at levels up to 109 ppm, "did not increase the overall toxicity of cigarette smoke" [Carmines, 2002].

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 acetanisole at 109 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].

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 acetanisole at levels up to 109 ppm (a multiple of its typical use in a US cigarette) [Roemer et al., 2002].

A mouse skin painting study investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including acetanisole at 250 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)].

When tested at 250 ppm in cigarettes, in a 13-week inhalation study, the presence of acetanisole "…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].

Information relating to the pyrolysis and/or transfer of acetanisole 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.

Additional information concerning the in vitro mutagenicity and genotoxicity 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 acetanisole at levels up to 144 ppm.

In vitro toxicity testing of tobacco ingredients in burnt form (Internal document R-21).

References - Emissions and Associated Toxicity Data

An Interim report on data originating from Imperial Tobacco Limited's Genotoxicity testing programme September 2003 – internal document

An updated report on data originating from Imperial Tobacco Limited's external Genotoxicity testing programme – Round 2 August 2007 – internal document

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, 77-9.

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

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

Internal document R-21. In vitro toxicity testing of tobacco ingredients in burnt form

ITL internal report titled: Report on the Thermochemical Properties of Ingredients.

Acetanisole

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.

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

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

Vanscheeuwijck et al., (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 4: Subchronic inhalation toxicity. Fd Chem Toxicol 40, 113-13.