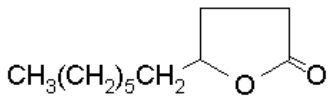
Undecalactone, gamma-

Ingredient synonym names

Aldehyde C-14
Aldehyde C-14 peach
Dihydro-5-heptyl-2(3H)-furanone
2(3H)-Furanone, 5-heptyldihydro-γ-Heptyl-γ-butyrolactone
γ-Heptylbutyrolactone
γ-n-Heptylbutyrolactone
5-Heptyldihydro-2(3H)-furanone
4-Hydroxyundecanoic acid lactone
4-Hydroxyundecanoic acid γ-lactone
Peach aldehyde
Peach lactone
Persicol
δ-Undecalactone
γ-Undecalactone
Undecanoic acid, 4-hydroxy-, γ-lactone
γ-Undecanolactone
γ-Undecanolide
Undecan-4-olide
1,4-Undecanolide
4-Undecanolide
4-Heptyl-4-hydroxybutanoic acid lactone
4-n-Heptyl-4-hydroxybutanoic acid lactone
γ-Heptyl-gamma-butyrolactone
γ-Undecyl lactone
Furanone, 5-heptyldihydro-
Heptylbutyrolactone
Hendecylene methyl lactone
Undecylene methyl lactone

IDENTIFIER DETAILS

Ingredient chemical structure



CAS Number	FEMA Number	Additive Number
104-67-6	3091	-
Ingredient EC Number	**FL Number**	**CoE Number**
203-225-4	10.002	179

Chemical formula C11H20O2

Ingredient CLP Classification

Ingredient REACH Registration Number

01-2119959333-34

Acute Oral Toxicity	Eye Damage/Irritation	Carcinogenity

Undecalactone, gamma-

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	297°C	Boiling Point	164 – 166°C @ 13mmHg (Sigma-Aldrich)

STATUS IN FOOD AND DRUG LAWS

Acceptable Daily Intake (ADI, mg/kg)	0 - 1.25
Acceptable Daily Intake (ADI) comments	No safety concern at current levels of intake when used as a flavouring agent - JECFA (1967) maintained 1997
FDA Status	C172.515: Synthetic flavouring substances and adjuvants

CoE limits - Beverages (mg/kg)	No data identified	CoE limits - Food (mg/kg)	No data identified	CoE limits - Exceptions (mg/kg)	No data identified

HUMAN EXPOSURE

Ingredient Natural Occurence (if applicable)

Reported found in hydrolysed soy protein, butter, peach, apricot, and passion fruit, fresh apple, guava fruit, fresh blackberry, heated butter, heated beef fat, pork fat, yellow passion fruit juice, cooked scented rice, origanum (Spanish) (Coridothymus cap. (L) Rchb.) mountain papaya, starfruit, plumcot and chicken fat (Fenaroli, 2005).

References - Ingredient Natural Occurence

Fenaroli’s Handbook of Flavor Ingredients (2005). Fifth Edition. CRC Press. ISBN: 0-8493-3034-3.

Ingredient Reported Uses

gamma-Undecalactone is reportedly used (maximum levels) in baked goods at 15.73 ppm, frozen dairy at 7.2

ppm, meat products at 0.1 ppm, soft candy at 16.53, gelatin, pudding at 9.87 ppm, non-alcoholic beverages at 6.22 ppm, alcoholic beverages at 5.66 ppm, hard candy at 11.34 ppm, and chewing gum at 174.9 ppm (Fenaroli, 2005).

References - Ingredient Reported Uses

Fenaroli's Handbook of Flavor Ingredients (2005). Fifth Edition. CRC Press. ISBN: 0-8493-3034-3.

TOXICITY DATA

In Vivo Data

Acute Toxicity Data

Rat - LD50, Oral, 18.5 g/kg

Jenner et al., (1964). Food flavourings and compounds of related structure 1: Acute oral toxicity. Food & Cosmetic Toxicology. 2: 327-343.

In Vivo Carcinogenicity/Mutagenicity

Groups of 20 male and 20 female rats were fed diets containing 0, 0.1, and 0.5 % γ-undecalactone (approximating to 50 and 250 mg/kg bw/day respectively) for two years. No adverse effects of treatment were reported, with no evidence of carcinogenicity in seven major organs during histological investigation in this study. (However, it should be noted that this study would not meet currently acceptable guidelines BIBRA, 1989).

References - In Vivo Carcinogenicity/Mutagenicity

BIBRA (1989). Toxicity Profile γ-Undecalactone.

Dermal Toxicity

Undecalactone was reported to be a severe irritant of rabbit skin, and moderately irritating to guinea pigs (no further information) (RTECS, 24/07/02).

When tested at 2 % in petrolatum in human volunteers, γ-undecalactone was reported to be neither an irritant nor sensitiser of human skin. However, in an earlier study, redness was reported to be seen in five of 136 subjects following 24 - 48 hour covered contact with 0.05 - 0.5 % γ-undecalactone in either a cream base or ethanol (BIBRA 1989).

References - Dermal Toxicity

BIBRA (1989). Toxicity Profile γ-Undecalactone

RTECS (Register of Toxic Effects of Chemical Substances). Search carried out on 24/07/02. RTECS No. YQ2485000.

Reproductive/ Developmental Toxicity

No data identified

References - Reproductive/ Developmental Toxicity

No data identified

Inhalation Toxicity

No data identified

References - Inhalation Toxicity

No data identified

Cardiac Toxicity

No data identified

References - Cardiac Toxicity

No data identified

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

The feeding of 13 - 115 mg/kg of γ-undecalactone to rats (strain not specified) for 5 - 9 days was reported to produce fatty infiltration of the liver parenchyma cells (JECFA 1967).

In a 12 week feeding study, rats were fed γ-undecalactone at 15.5 mg/kg for 90 days, a slight alteration in blood cellular composition of the females was reported (exact parameter was not specified). No other adverse effects were reported in the females with no treatment related effects being reported for the males (JECFA 1967, 1998).

Linear aliphatic hydroxycarboxylic acids are reported to be hydrolysed and rapidly metabolised via the fatty acid synthesis pathway. Linear saturated 5 hydroxycarboxylic acids are reportedly formed from γ-lactones, are converted by acetyl coenzyme A to hydroxythioesters, which then undergo γ-oxidation to and cleavage to form an acetyl CoA fragment and a new γ-hydroxythioester reduced by two carbon atoms [Adams et al., 1998].

Doses in the region of the LD50 were reported to cause central nervous system depression to rats [Jenner, 1964].

Five types of odorous substances (Japan--beta-phenyl ethyl alcohol, methyl cyclopentenolone, isovaleric acid, gamma-undecalactone, and scatol) were tested for olfactory response in the standard olfactory acuity test among dysosmia patients (n=1952). Olfactory dysfunctions included chronic paranasal sinusitis, allergic rhinitis, common cold sequela, complications from head injuries, drug-induced dysosmia, congenital dysosmia, and dysosmia of unknown etiology. The standard olfactory acuity test before treatment indicated that 82 patients detected only one odor within the detection threshold and 157 within the recognition threshold; 40 responded only to isovaleric acid

at the detection threshold and 101 at the recognition threshold. No specific trends were noted in etiologies of dysosmia that allowed smelling of isovaleric acid only either at the detection or recognition threshold. The difference in olfactory response of patients with olfactory dysfunction such as those above may be due to variations in the number of olfactory receptor proteins for specific odors within olfactory cells or different responses to the type of molecules of odor-emitting substances [Shibuya et al., 2002].

References - In Vivo - Other Relevant Studies

Adams et al., (1998). The FEMA GRAS Assessment of Lactones Used as Flavour Ingredients. Food & Chemical Toxicology. 36: 249-278.

JECFA, (1967). Safety evaluation of certain food additives and contaminants. Prepared by the 49th meeting of the Joint FAO/WHO Expert Committee on Food Additives.

JECFA, (1998). Safety evaluation of certain food additives and contaminants. Prepared by the 49th meeting of the Joint FAO/WHO Expert Committee on Food Additives.

Jenner et al., (1964). Food flavourings and compounds of related structure 1: Acute oral toxicity. Food & Cosmetic Toxicology. 2: 327-343.

Shibuya E et al., (2002). Study on difference in olfactory response in dysosmia patients. Nippon Jibiinkoka Gakkai Kaiho 105(7): 783-9 (Article in Japanese).

In Vitro Data

In Vitro Carcinogenicity/Mutagenicity

γ-Undecalactone was reported to be negative in the Ames Salmonella assay with strains TA97 and TA100 both with and without metabolic activation at concentrations between 0.001 - 0.1 mg/plate [Fujita et al., 1987].

γ-Undecalactone was not mutagenic to Salmonella typhimurium in the Ames assay with the strains TA92, TA94, TA100, TA1535 and TA1537 in presence of a metabolic activation system, when tested up to 5 mg/plate (Ishidate et al., 1984; Hayashi et al., 1988). Similarly, negative results were seen in Escherichia coli (probably in the absence of a S9 fraction) [Yoo, 1986].

However, some evidence of DNA damage was seen in a Rec assay in the bacteria Bacillus subtilis with metabolic activation only [Kuroda et al., 1983; Yoo, 1986].

γ-Undecalactone did not induce chromosomal damage in a Chinese hamster lung fibroblast cell line, when tested up to 0.5 mg/ml in the absence of a metabolic activation system (Ishidate, 1988). γ-Undecalactone was reported not to be mutagenic in the micronucleus assay with six ddy mice injected with up to 2000 mg/kg via the intraperitoneal route [Hayashi et al., 1988].

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”.

References - In Vitro Carcinogenicity/Mutagenicity

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

Fujita, H. & Sasaki, M. (1987) Mutagenicity test of food additives with Salmonella typhimurium TA97 and TA102. II. Annu. Rep. Tokyo Metrop. Res. Lab. P.H., 38: 423-430.

Hayashi et al., (1988). Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. Food & Chemical Toxicology 26(6): 487-500.

Ishidate et al. (1984). Primary mutagenicity screening of food additives currently used in Japan. Food & Chemical Toxicology 22: 623.

Kuroda et al., (1983). Rec-assay of food additives. Nippon Kosnu Eisei Zasshi, 31: 277-281.

Yoo (1986). Mutagenic and antimutagenic activities of flavouring agents used in foodstuffs. J. Osaka Cy. Med. Cent. 34: 267.

In Vitro - Other Relevant Studies

γ-Decalactone (similar in structure to γ-undecalactone) was reported to be a potent inhibitor of mouse CYP2A5 but was reported to be a much less potent inhibitor of the human equivalent CYP2A6. CYP2A6 and the mouse equivalent CYP2A5 are reported to be responsible for the bioactivation of some promutagens and procarcinogens [Juvonen et al., 2000].

References - In Vitro - Other Relevant Studies

Juvonen et al., (2000). Pronounced differences in inhibition potency of lactone and on-lactone compounds for mouse and human coumarin 7-hydroxylases (CYP2A5 and CYP2A6). Xenobiotica 30(1): 81-92.

Emissions and Associated Toxicity Data

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 gamma-undecalactone at levels up to 3 ppm, "did not increase the overall toxicity of cigarette smoke" (Carmines, 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 gamma-undecalactone 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 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 13 wk 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.

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 gamma-undecalactone at 3 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 γ-undecalactone at 23 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 γ undecalactone 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].

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 gamma-undecalactone at levels up to 12 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

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 gamma-undecalactone at levels up to 3 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 γ-undecalactone at 23 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].

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 Undecalactone gamma at levels up to 127 ppm (Internal document R-53).

Information relating to the pyrolysis and/or transfer of gamma-undecalactone 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.

Undecalactone, gamma-

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 behaviour of these compounds during combustion on the cigarette, and allow estimation of the degree of intact transfer into the mainstream smoke. Under pyrolysis γ-undecalactone was found to transfer 99.2% intact, other breakdown product included dimethylhydroxyheptanoic acid (0.4%), butyl octanoate (0.3%) and heptanal (0.1%)

References - Emissions and Associated Toxicity Data

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.

Baker and Bishop, (2004). The pyrolysis of tobacco ingredients. J. Anal. Appl. Pyrolysis. 71: 223-311.

Carmines E. L. (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 1: Cigarette design, testing approach, and review of results. Food and Chemical Toxicology 40: 77-91.

In vitro toxicity testing of tobacco ingredients in burnt form (Internal document R-53).

Report on Thermochemical Properties of Ingredients – Internal document

Renne, R.A., Yoshimura, H., Yoshino, K., Lulham, G., Minamisawa, S., Tribukait. Dietz, D.D., Lee, K.M., Westerberg, R.B. (2006). Effects of flavouring and casing ingredients on the toxicity of mainstream cigarette smoke in rats. Inhalation Toxicology. 18:685-706.

Roemer et al., (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 3: In vitro genotoxicity and cytotoxicity. Food and Chemical Toxicology 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. Food and Chemical Toxicology 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: Sub chronic inhalation toxicity. Food and Chemical Toxicology 40: 113-131.