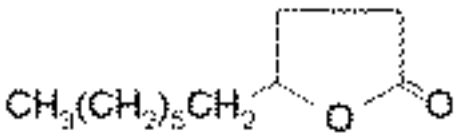
GAMMA-UNDECALACTONE

SYNONYMS

Aldehyde C-14
Aldehyde C-14 peach
Dihydro-5-heptyl-2(3*H*)-furanone
2(3*H*)-Furanone, 5-heptyldihydro-γ-Heptyl-γ-butyrolactone
γ-Heptylbutyrolactone
γ-*n*-Heptylbutyrolactone
5-Heptyldihydro-2(3*H*)-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

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_{11}H_{20}O_2$

IDENTIFIER DETAILS

CAS Number	:	104-67-6
CoE Number	:	179
FEMA	:	3091
EINECS Number	:	203-225-4

E Number :

SPECIFICATIONS

Melting Point: 297 C (Chemfinder 2002)

Boiling point: 164 – 166 C @ 13mmHg (Sigma-Aldrich)

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
0 - 1.25	JECFA	1967 (maintained in 1997)	No safety concern at current levels of intake when used as a flavouring agent

FDA Status: (CFR21)

Section Number	Comments
C172.515	Synthetic flavouring substances and adjuvants

HUMAN EXPOSURE

Natural Occurrence: 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).

Reported Uses: gamma-Undecalactone is reportedly used (maximum levels) in baked goods at 15.7 3 ppm, frozen dairy a t 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 a t 5.66 ppm, hard candy at 11.34 ppm, and chewing gum at 174.9 ppm (Fenaroli, 2005).

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 o n 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 st udy. 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 flavour ing 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.

In Vivo Toxicity Status

Species	Test Type	Route	Reported Dosage
Rat	LD_{50}	Oral	18.5 g/kg [Jenner et al., 1964]
Rabbit	Irritation (severe)	Dermal	100 mg/24h
Guinea Pig	Irritation (moderate)	Dermal	100 mg/24h [RTECS, 24/07/02]

The feeding of 13 - 115 mg/kg of -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 -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).

Carcinogenicity and Mutagenicity

Groups of 20 male and 20 female rats were fed diets containing 0, 0.1, and 0.5 % -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).

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, -undecalactone was reported to be neither an irritant nor sensitiser of human ski n. 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 % -undecalactone in either a cream base or ethanol (BIBRA 1989).

Inhalation toxicity

A recent study investiga ted 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 cig arette. 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 -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 ind icated that addition of -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].

Other Relevant Studies

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

Doses in the region of the LD_{50} 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].

Behavioural data

No data identified.

***In Vitro* Toxicity Status**

Carcinogenicity and Mutagenicity

-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].

-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].

-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). -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].

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 th e 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 dif ferent combinations to reference cigarettes. The addition of - 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 re d 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 Genotoxici ty 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 *Undecalactone gamma* at levels up to 127 ppm.

Other relevant studies

-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 pote nt 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].

PYROLYSIS AND TRANSFER STUDIES

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.

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 beha viour 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 br eakdown product included dimethylhydro xyheptanoic acid (0.4 %), butyl octanoate (0.3%) and heptanal (0.1%).

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