DELTA-DECALACTONE

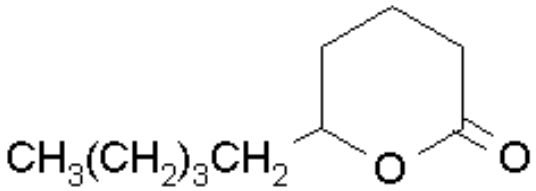
SYNONYMS

1,5-Decanolide
5-Decanolide
5-hydroxy Decanoic acid-delta-lactone
Amyl-delta-valerolactone
Decan-5-olide
Decanolide-1,5
Pentyl-delta-valerolactone

CHEMICAL FORMULA

$C_{10}H_{18}O_2$

CHEMICAL STRUCTURE



IDENTIFIER DETAILS

CAS Number	:	705-86-2
CoE Number	:	621
FEMA	:	2361
EINECS Number	:	211-889-1
E Number	:	-

CLP CLASSIFICATION

Ingredient CLP Classification: No

Endpoint	Classification	Category
Acute Oral Toxicity	-	-
Acute Dermal Toxicity	-	-
Acute Inhalation Toxicity	-	-
Skin Corrosive/irritant	-	-
Eye Damage/Irritation	-	-
Respiratory Sensitisation	-	-
Skin Sensitisation	-	-
Mutagenicity/Genotoxicity	-	-
Carcinogenicity	-	-
Reproductive Toxicity	-	-
Specific Target Organ Toxicity	-	-
Aspiration Toxicity	-	-

SPECIFICATIONS

Melting Point: -27°C

Boiling point: 281°C

Smiles Code: O1[C@@H](CCCC1=O)CCCCC

PURPOSE

Flavouring substance.

STATUS IN FOOD, TOBACCO AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
5	20	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
Acceptable	JECFA	1997	No safety concerns at current levels of intake when used as a flavouring agent

FDA Status:[CFR21]

Section Number	Comments
172.515	Synthetic flavouring substances and adjuvants

HUMAN EXPOSURE

Natural Occurrence: Delta-decalactone is reported to be found in coconut and raspberry. Delta-decalactone is reported to be ubiquitous in food occurring mainly in fruits and berries, alcoholic beverages, meat and dairy products with reported levels of raspberry 0.005-1.4 mg/kg, other fruits up to 0.15; butter 0.85-7.95 ppm; white wine 0.06 mg/kg; rum 0.02 mg/kg and coconut 0.1-97 mg/kg [Fenaroli 2005; Adams *et al.,* 1998; CoE 2000].

Glucuronide and sulphate conjugates are of δ-decalactone have reportedly been identified in cow's milk and in cow's milk fat, butter fat and kidney fat [Opdyke, 1976].

Reported Uses: Delta-decalactone is reportedly used in baked goods at 26.4 ppm, fats, oil at 19.7 ppm, frozen dairy at 37.06 ppm, soft candy at 25.63 ppm, confection, frosting at 5 ppm, sweet sauce at 0.13 ppm, gelatin, pudding at 29.62 ppm, non-alcoholic beverages at 13.69 ppm, alcoholic beverages at 6.5 ppm, gravies at 8 ppm [Fenaroli, 2005].

Sources other than foods: Delta-decalactone is reportedly found in the mandibular glands of the ant *Neopenera apicalis* [Cruz Lopez, 1997].

TOXICITY DATA

This ingredient has been registered under REACH. Under REACH, registrants have an obligation to provide information on substances they manufacture 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 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 δ-decalactone at levels up to 6 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 δ-Decalactone at 6.5 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 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 reference 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 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

LD_{50}	rat	oral	>4300 mg/kg
Mild	rabbit	eyes	100 mg
Mild	rabbit	skin	500 mg/24 hr

RTECS (23/07/02)

Carcinogenicity and Mutagenicity

δ-Decalactone 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].

Dermal Toxicity

δ-Decalactone was reported to be slightly irritating when applied neat and occluded to intact or abraded rabbit's skin for 24 hours [Opdyke 1976]. There was reported to be no irritation to human subjects after 48 hours of occluded contact, with a 1% concentration of δ-decalactone in petrolatum [Kligman, 1975]. No sensitisation reactions were reported for 25 human volunteers exposed to a 1% concentration of δ-decalactone in petrolatum using a maximisation procedure [Kligman, 1975].

Reproductive / Developmental Toxicity

No data identified.

Inhalation Toxicity

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 δ-decalactone at 6 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 δ-Decalactone at 18 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 δ-Decalactone 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

No effects of treatment and no histological findings were reported in a 49 week toxicity study in rats that were exposed to a mixture of 150 mg/kg/day of δ-decalactone and 300 mg/kg/day δ-dodecalactone added to the diet [Wilson 1961]. A mixture of 75 mg/kg/day of δ-decalactone and 150 mg/kg/day δ-dodecalactone added to the diet of beagle dogs for 38 weeks, there was

reported to be no effect of treatment upon any of the blood, biochemical or urinalysis values determined [Wilson, 1961].

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 δ-lactones, are converted by acetyl coenzyme A to hydroxythioesters, which then undergo β-oxidation and cleavage to form an acetyly CoA fragment and a new β-hydroxythioester reduced by two carbon atoms [Adams *et al.,* 1998].

In Vitro Toxicity Status

Carcinogenicity and Mutagenicity

δ-Hexalactone [a structurally similar compound to δ-decalactone] was reported to be negative in the Ames *S. typhimurium* assay with strains TA98, 100, 102, 1535 and 1537 [Kawachi *et al.,* 1981].

δ-Hexalactone was reported not to induce sister chromatid exchanges in the hamster lung fibroblast cells [Kawachi *et al.,* 1981].

δ-Hexalactone was reported to be negative in a rec-assay, using *Bacillus subtilis* [Kawachi *et al.,* 1981].

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, 100, 102, 1535 and 1537 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 δ-decalactone at levels up to 6 ppm [a multiple of its typical use in a US cigarette] [Roemer *et al.,* 2000].

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 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 *delta-decalactone* at levels up to 127 ppm.

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 δ-Decalactone at 18 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].

Other Relevant Studies

No data identified.

PYROLYSIS AND TRANSFER STUDIES

Information relating to the pyrolysis and/or transfer of delta-decalactone 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 behaviour of these compounds during combustion on the cigarette, and allow estimation of the degree of intact transfer into the mainstream smoke. Under pyrolysis delta-Decalactone was found to transfer 97.5% intact, other breakdown product included gamma-Tetradecalactone (0.8%), Heptanal (0.5%), Methoxyethyl Acetate (0.4%), gamma-Octalactone (0.4%), gamma-Undecalactone (0.2%), and Octanal (0.2%).

REACH Statement

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

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