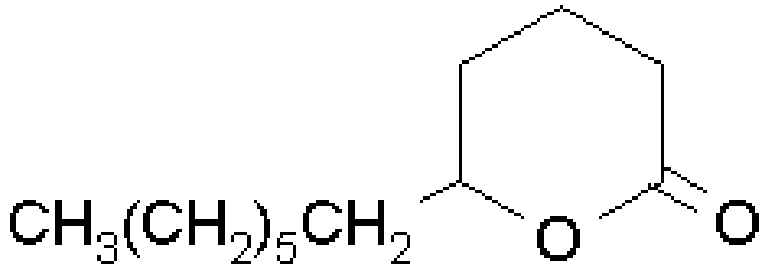
DELTA-DODECALACTONE

SYNONYMS

1,5-dodecanolactone
Dodecan-s-olide
2H-Pyran-2-one, 6-heptyltetrahydro-
n-Heptyl-delta-valerolactone
5-Hydroxydodecanoic acid lactone
5-Hydroxydodecanoic acid delta lactone
Dodecanoic acid

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_{12}H_{22}O_2$

IDENTIFIER DETAILS

CAS Number	:	713-95-1
CoE Number	:	624
FEMA	:	2401
EINECS Number	:	211-932-4
E Number	:	-

SPECIFICATIONS

Melting Point: -12^{o}C

Boiling point: 140 - 141^{o}C

PURPOSE

Flavouring substance.

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
-	40	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
ACCEPTABLE	JECFA	1997	No safety concern at current levels of intake when used as a flavouring substance.

FDA Status:[CFR21]

Section Number	Comments
172.515	Synthetic flavouring substances and adjuvants

HUMAN EXPOSURE

Natural Occurrence: Delta-dodecalactone is reported found in several natural products including, butter, coconut milk, cream and milk, peach, raspberry, strawberry, peppermint oil, fresh blackberry, blackberry (heated), strawberry jam, blue cheeses, cheddar cheese, swiss cheeses, camembert cheese, parmesan cheese, chicken fat, heated beef fat, boiled mutton, lamb and mutton liver, pork fat, white wine, sherry, fresh plum and raw beans [Fenaroli, 2005].

Reported Uses: Delta-dodecalactone is reportedly used in baked goods at 20 ppm, breakfast cereals at 3.3 ppm, fats, oils, at 40 ppm, milk products at 1 ppm, cheese at 3.8 ppm, frozen dairy at 1 ppm, fruit juice at 0.0001 ppm, meat products at 9 ppm, condiment relish at 0.1 ppm, soft candy at 200 ppm, confection, frosting at 2 ppm, gelatin pudding at 6.98 ppm, non-alcoholic beverages at 4.2 ppm, alcoholic beverages at 2.07 ppm. [Fenaroli, 2005]. Raspberry 0.3 mg/kg, [Other fruits up to 100.25 mg/kg], butter 2.55 - 24.2 mg/kg, coconut 0.1-60 mg/kg, [COE, 2000].

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 delta-dodecalactone at levels up to 2 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 delta-dodecalactone 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 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	> 5 g/kg
Rabbit	LD_{50}	Skin	> 5 g/kg [RTECS, 2002]

A 49-week study in rats and a 38-week study in dogs where a mixture of *delta*-dodecalactone and *delta*–decalactone was added to the diet of test animals providing an average daily intake of 300 mg/kg and 150 mg/kg respectively revealed 'no effects' [no pathology or histology was discussed] similarly a 38-week study in dogs revealed a NOEL of 150 mg/kg, [Adams *et al*., 1998].

Dermal toxicity

Similarly, a recent mouse skin painting study investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including Delta-dodecalactone at 2 ppm. The authors concluded that the study "did not indicate any substantive effect of these ingredients on the tumourogenicity of cigarette smoke condensate" [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].

Opdyke, (1979), reported than technical grade *delta*–dodecalactone applied to rabbit skin [intact or abraded] did not produce any signs of irritation however, application of full strength *delta*–dodecalactone to rabbit skin under occlusion was reported to be moderately irritating. Human subjects tested with 12 %

delta–dodecalactone in petrolatum [48 hour closed patch] showed no signs of irritation, [Opdyke, 1979].

No sensitisation was observed in an unknown number of male guinea-pigs injected intradermally with 0.1ml of a 0.1 % suspension [suspended in propylene glycol-saline] and later challenged with the same dose. Similarly a maximisation test with 30 volunteers [12 % in petrolatum] produced no sensitisation reactions [Opdyke, 1979].

Application of 0.1 ml *delta*–dodecalactone [unknown concentration] into the rabbit eye was reported to cause no injury to the cornea or conjunctiva in a 24 hour period [Opdyke, 1979].

delta–dodecalactone at 25 % in 95 % ethanol did not cause photochemical irritation of rabbit skin exposed to UV-A [λ365 nm] for 30 minutes at a specified distance of 10 - 15 cm, [Opdyke, 1979].

Inhalation toxicology

When tested at 2 ppm in cigarettes, in a 13-week inhalation study, the presence of delta-dodecalactone "…had no discernible effect on the character of extent of the biologic responses normally associated with inhalation of mainstream cigarette smoke in rats, [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].

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 delta-dodecalactone at 2 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 delta-dodecalactone at 164 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 delta-dodecalactone 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]

Behavioural data

No data identified

Other relevant studies

The estimated per capita in take for *delta* -dodecalactone in the USA is 1.14 mg/person per day [19 μg/kg per day] and 6.8 mg/person [113 μg/kg per day] in Europe and has been reported to be of no safety concern based on the current levels of intake [WHO, 1998].

The linear aliphatic hydroxy carboxylic acids are reported to be hydrolysed and rapidly oxidized via the fatty acid pathway, [Adams *et al*., 1998].

A study in which rats were fed $^{14}C_1$ -γ-decalactone and $^{14}C_1$ -γ-dodecalactone revealed that both were metabolised in a similar way to $^{14}C_1$- lauric acid, with around 75 % of the labelled carbon being eliminated as carbon dioxide within 24 hours [Adams, 1998].

When assayed as a spasmogenic agent in hamster colon *delta*–dodecalactone was observed to be in active [dose not stated] [Opdyke, 1979].

In Vitro Toxicity Status

Carcinogenicity and mutagenicity

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 delta-dodecalactone at levels up to 2 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 delta-dodecalactone at 164 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].

Delta dodecalactone was observed to totally inhibit outgrowth of *B. cinerea* or *Sclerotinia sp.* Sc4 mycelia from an inoculum agar plug at 0.1 % [v/v], however, delta dodecalactone vapours were without effect on the germination of lettuce seed, [Parker *et al*., 1997].

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 dodecalactone at levels up to 7 ppm [In vitro toxicity testing of tobacco ingredients in burnt form (Internal document R-45)].

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".

PYROLYSIS AND TRANSFER STUDIES

Information relating to the pyrolysis and/or transfer of delta -*dodecalactone* 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.

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