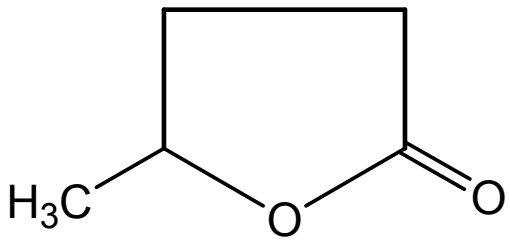
GAMMA-VALEROLACTONE

SYNONYMS

Pentan-4-olide
4-Methylbutyrolactone
4-Valerolactone
4-Hydroxypentanoic acid lactone
Dihydro-5-methyl-2(3H)-furanone

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_5H_8O_2$

IDENTIFIER DETAILS

CAS Number	:	108-29-2
CoE Number	:	757
FEMA	:	3103
EINECS Number	:	203-569-5
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: -31°C [at 760 mm / Hg]

Boiling point: 207 - 208°C

PURPOSE

Flavouring compound.

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (ppm)	Food (ppm)	Exceptions (mg/kg)
3 [JECFA, 2005]	20 [JECFA, 2005]	-

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
-	-

HUMAN EXPOSURE

Natural Occurrence: Reported to be found in boiled beef, beef fat, beer, cacao, Swiss cheese, ground and roasted coffee, roasted filberts, milk fat, dried mushroom, peach, roasted peanuts, heated pork fat, black tea, yogurt,

strawberry jam, tomato, wheaten bread, Gruyere cheese, heated butter, cooked beef, white wine, red wine, coffee, and bourbon vanilla (Fenaroli, 2005).

Reported Uses: gamma-Valerolactone is reportedly used (maximum levels) in baked goods at 147.5 ppm, frozen dairy at 18.05 ppm, meat products at 13 ppm, condiments & relishes at 2.6 ppm, gelatins & puddings at 29.84 ppm, non-alcoholic beverages at 29.6 ppm, soft candy at 147.80 ppm, and alcoholic beverages at 4.25 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 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 γ-valerolactone at levels up to 2639 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-valerolactone 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 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

Species	Test Type	Route	Reported Dosage
Rat	LD_{50}	Oral	>5g/kg
Rat	LD_{50}	Oral	8.8ml/kg
			[Opdyke and Letizia, 1983]

Guinea Pig	LD_{LO}	Intramuscular	2500mg/kg
Rabbit	LD_{50}	Oral	2480mg/kg [JECFA 1998]

JECFA, (1998), reporting on a safety evaluation of certain food additives, stated that γ-valerolactone at current levels of intake [*per capita* intake in Europe: 140 µg / day] had 'no safety concerns' [JECFA, 1998].

Carcinogenicity and Mutagenicity

Limited studies suggest that γ-valerolactone was neither carcinogenic, nor inhibited benzo[*a*]pyrene induced neoplasms of the forestomach in mice [Opdyke & Letizia, 1983].

A mouse skin painting study investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including γ-valerolactone at 1 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)] [Gaworski *et al.*, 1999].

Dermal toxicity

γ-Valerolactone was reported as a slight irritant to rabbit skin, but at 10% in petrolatum it was neither an irritant nor sensitizer of the skin of human volunteers [Opdyke & Letizia, 1983].

Inhalation toxicity

When tested at 1 ppm in cigarettes, in a 13-week inhalation study, the presence of γ-valerolactone "…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].

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 γ-valerolactone at 2639 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-valerolactone at 25 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-valerolactone 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-Valerolactone at levels up to 3 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Other Relevant Studies

Rats fed 10,000 ppm γ-valerolactone for 13 weeks were reported to have suffered no adverse effects on growth or haematology [Opdyke & Letizia, 1983].

Krasavage *et al.*, (1978) reported on the neurotoxicity of methyl *n*-butyl ketone, the parent compound of γ-valerolactone. Methyl *n*-butyl ketone is reported by the authors as a known neurotoxin which can induce peripheral polyneuropathy in humans. One of the metabolites of methyl *n*-butyl ketone is γ-valerolactone. γ-Valerolactone was administered to male rats in drinking water or by gavage. The doses in drinking water ranged from 0.25 to 1%, and doses given by gavage were from 200 to 1200 mg / kg. Appropriate controls were included. [no times were stated]. There were no neurotoxic effects reported for γ-valerolactone [Krasavage *et al*., 1978].

Behavioural data

No data identified

***In Vitro* Toxicity Status**

Carcinogenicity and Mutagenicity

A series of FEMA GRAS lactones used as flavour ingredients, including γ-butyrolactone which is structurally related to γ-valerolactone, were analysed for genotoxic potential. The authors [a FEMA Expert Panel] state that [based on 36 genotoxicity studies] γ-butyrolactone 'is not mutagenic and that isolated

positive results performed in non-standard assays at high solution concentrations are not compelling evidence of genotoxic potential'. The authors additionally stated that 'the negative response in repeated *Salmonella* mutagenicity assays supports the Panel's conclusion that exposure to γ-butyrolactone exhibits little potential for interaction with DNA' [Adams *et al*., 1998].

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 γ-valerolactone at levels up to 2639 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–valerolactone at 25 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].

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".

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

PYROLYSIS AND TRANSFER STUDIES

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