Citral

Botanical Source

Synonyms	DIMETHYL-OCTA-2,6-DIENAL(3,7-); GERANIAL; NERAL; CITRAL a; CITRAL b; CITRAL (trans-); CITRAL (cis-)
IUPAC Name	3,7-DIMETHYL-OCTA-2,6-DIENAL
CAS Reference	5392-40-5 106-26-3
E Number	

Food Legislation

Council of Europe (CoE)	
Number	Comment
109	Listed by the Council of Europe as acceptable for use in food.

US Food and Drug Administration	
Number	Comment
182.60	Approved by the US FDA. FDA 21 CFR 182.60

Joint FAO/WHO Expert Committee on Food Additives (JECFA)		
Number	ADI	Comment
-	ADI 0-0.5 MG/KG BW	-

FEMA	
FEMA No.	Comment
2303	Generally recognised as safe as a flavour ingredient:GRAS List Number 3

Natural Occurrence and Use in Food
Found in grapefruit juice, orange, orange juice, celery, apricot, blackcurrants, grape, hops, kiwi fruit, mango, mango ginger, melon, plum, raspberry, rum; used in baked goods, candy, ice cream.

Estimated Intake from Food and Drink	
Daily Intake mg/kg/day	FEMA Possible Average Daily Intake mg
0.05	25.27

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Tobacco Product Related Chemical and Biological Studies for Ingredients Added in a Mixture

Smoke Chemistry		
Published Source	Level Tested %	Comment
BAT	0.00200	At maximum application level this ingredient is not associated with significant increases in levels of Hoffmann analytes in smoke.
Philip Morris	0.00010	An overall assessment of the data suggests that this ingredient did not add to the toxicity of smoke.

Ames Activity		
Published Source	Level Tested %	Comment
BAT	0.00200	Within the sensitivity and specificity of the system the Ames activity of the cigarette smoke condensate was not increased by the addition of the ingredient.
Philip Morris	0.00010	Within the sensitivity and specificity of the system the Ames activity of the cigarette smoke was not increased by the addition of the ingredient.

Micronucleus		
Published Source	Level Tested %	Comment
BAT	0.00200	Within the sensitivity of the in vitro micronucleus assay the activity of the cigarette smoke condensate was not increased by the addition of the ingredient.

Neutral Red		
Published Source	Level Tested %	Comment
BAT	0.00200	Within the sensitivity of the test system the in vitro cytotoxicity of the cigarette smoke condensate was not increased by the addition of the ingredient.
Philip Morris	0.00010	Within the sensitivity of the test system the in vitro cytotoxicity of the cigarette smoke was not increased by the addition of the ingredient.

Inhalation		
Published Source	Level Tested %	Comment

BAT	0.00200	The results indicate that the addition of the ingredient had no discernible effect on the inhalation toxicity of mainstream smoke.
Philip Morris	0.00010	The data indicate that the addition of the ingredient, when added with one of three groups, did not increase the inhalation toxicity of the smoke.

Mouse Skin Painting		
Published Source	Level Tested %	Comment

References
Baker RR, Pereira da Silva JR, Smith G. The effect of tobacco ingredients on smoke chemistry. Part I: Flavourings and additives. Food Chem Toxicol. 2004; 42 Suppl:S3-37.
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Carmines EL. Evaluation of the potential effects of ingredients added to cigarettes. Part 1: cigarette design, testing approach, and review of results. Food Chem Toxicol. 2002; 40(1): 77-91.
Rustemeier K, Stabbert R, Haussmann HJ, Roemer E, Carmines EL. Evaluation of the potential effects of ingredients added to cigarettes. Part 2: chemical composition of mainstream smoke. Food Chem Toxicol. 2002; 40(1): 93-104.
Roemer E, Tewes FJ, Meisgen TJ, Veltel DJ, Carmines EL. Evaluation of the potential effects of ingredients added to cigarettes. Part 3: in vitro genotoxicity and cytotoxicity. Food Chem Toxicol. 2002; 40(1): 105-111.
Vanscheeuwijck PM, Teredesai A, Terpstra PM, Verbeeck J, Kuhl P, Gerstenberg B, Gebel S, Carmines EL. Evaluation of the potential effects of ingredients added to cigarettes. Part 4: subchronic inhalation toxicity. Food Chem Toxicol. 2002; 40(1): 113-131.

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Tobacco Product Related Chemical and Biological Studies for Ingredients Tested Singly

References
Baker RR, Bishop LJ. The pyrolysis of tobacco ingredients. J. Anal. Appl. Pyrolysis 2004, 71, 223-311.
Gaworski CL, Vollmuth TA, York RG, Heck JD, and Aranyi C. Developmental toxicity evaluation of inhaled citral in Sprague-Dawley rats. Food Chem Toxicol. 1992, 30(4):269-75.

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Toxicological Data on the Unburnt Ingredient

[+ve, positive; -ve, negative; ?, equivocal; with, with metabolic activation; without, without metabolic activation]

In vivo

Species	Test conditions	Endpoint	Result	Reference
Mouse Groups of 10 male and 10 female B6C3F1	Administered in the diet at 0, 3,900, 7800, 25600 or 31300 ppm for 14 weeks. The maximum tested doses were 7.5-8.1 g/kg bw/day, which produced overt signs of toxicity Micronuclei were measured in the erythrocytes of the peripheral blood sampled 24 hours after the end of the 14-week treatment period.	Chromosomal damage	-ve A high quality study	NTP, 2003
Mouse Groups of 4-5 male B6C3F1	A daily ip injection of 0, 250, 500 or 750 mg/kg bw was given for 3 days. Doses of 1000 mg/kg bw/day were lethal. Micronuclei were measured in the erythrocytes in the bone marrow 24 hours after the last injection.	Chromosomal damage	-ve There was a slight treatment-related increase in micronuclei (0.5/1000 cells in the controls compared with 1.1-1.75/1000 cells in the 3 treatment groups), but no clear relationship with dose.	NTP, 2003

In vitro

Test system	Test conditions	Endpoint	Activation	Result	References
Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537	Up to 160 µg/plate	Mutation	With and without rat and hamster liver S9	-ve a high quality study	NTP, 2003
Salmonella typhimurium strains TA92, TA94, TA98, TA100, TA1535, TA1537	Up to 100 µg/plate (the highest dose that was not toxic)	Mutation	With and without rat liver S9	-ve	Ishidate *et al.* 1984
Salmonella typhimurium strains TA97a, TA98, TA100, TA102	Up to 700 µg/plate	Mutation	With and without rat liver S9	-ve	Gomes-Carneiro *et al.* 1998 (Toxline abstract)
Escherichia coli WP2 uvrA (trp$^-$)	100 µg/plate	Mutation	No information in the secondary source	-ve (Japanese paper, with English summary and tables)	Yoo, 1986 (cited in JECFA, 2001)
Bacillus subtilis strains M45 and H17	Tested at 2.5 µL/disc in a rec assay measuring differential toxicity	DNA damage (indicative test)	No information in the secondary source	+ve (Japanese paper, with English summary and tables)	Yoo, 1986 (cited in JECFA, 2001)
Bacillus subtilis strains M45 and H17	Tested at 17 µg/disc in a rec assay measuring differential toxicity	DNA damage (indicative test)	No information in the secondary source	-ve (Japanese paper, with English summary and tables)	Oda *et al.* 1979 (cited in JECFA, 2001)

Chinese hamster ovary cells	Cells were exposed to a maximum of 40 µg/mL for 26 hours and then examined for sister chromatid exchange	Chromosome effects	With and without rat liver S9	+ve (a dose-related increase without S9, and a treatment-associated increase in the presence of S9) A high quality study	NTP, 2003
Chinese hamster ovary cells	Test concentration of up to 61 µg/mL Cells were exposed for 10.5 hours in the absence of S9 (or for 2 hours in its presence) and examined for chromosome aberrations	Chromosome damage	With and without rat liver S9	-ve A high quality study	NTP, 2003
NCTC 929 cell line derived from mouse fibroblasts	The cells were exposed to a maximum of 30 µg/mL for up to 17 hours Measurement of tumour suppressor protein p53	An indication of DNA damage	Without The cells were said to have some inherent metabolic capability.	+ve a very clear dose-related increase in p53 induction throughout the tested concentration range. An unvalidated protocol	Duerksen-Hughes *et al.* 1999

References

Duerksen-Hughes PJ *et al* (1999). p53 Induction as a genotoxic test for twenty-five chemicals undergoing *in vivo* carcinogenicity testing. Environmental Health Perspectives 107, 805-812.

Gomes-Carneiro M R *et al* (1998). Mutagenicity testing (+/-)-camphor, 1,8-cineole,

citral, citronellal, (-)-menthol and terpineol with the Salmonella/microsome assay. Mutation Research 416, 129-36 (cited in Toxline and CCRIS).

Ishidate M Jr *et al* (1984). Primary mutagenicity screening of food additives currently used in Japan. Food and Chemical Toxicology, 22, 623–636.

Oda Y *et al* (1979). Mutagenicity of food flavours in bacteria. Osaka-Furitsu Koshu Eisei Kenyu, 9, 177 (cited in JECFA, 2001).

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