

Tetramethyl pyrazine (2,3,5,6-)

Botanical Source

Synonyms Tetramethylpyrazine

IUPAC Name

CAS Reference 1124-11-4

E Number

Food Legislation

Council of Europe (CoE)

Number	Comment
734	Listed by the Council of Europe as acceptable for use in food at up to 5 ppm.

US Food and Drug Administration

Number	Comment
-	-

Joint FAO/WHO Expert Committee on Food Additives (JECFA)

Number	ADI	Comment
780	8	No safety concern at current levels of intake when used as a flavouring agent.

FEMA

FEMA No.	Comment
3237	Generally recognised as safe as a flavour ingredient:GRAS List Number 3

Natural Occurrence and Use in Food

Found in wheat bread, sake, shrimp, beef, beer, coffee, peanut; used in baked goods, dairy products, candy.

Estimated Intake from Food and Drink

Daily Intake mg/kg/day	FEMA Possible Average Daily Intake mg
0.00003248	0.686

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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	0.00240	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	0.00240	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	0.00240	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.
Lorillard	0.00001	The results indicate that the addition of the ingredient had no discernible effect on the inhalation toxicity of mainstream smoke.
Philip Morris	0.00240	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
Lorillard	0.00001	None of the changes appeared to be substantial enough to conclude that the tumour promotion capacity of the condensate was discernibly different between condensate produced from cigarettes with the ingredient in comparison with condensate from cigarettes without the ingredient.

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.
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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.

Gaworski CL, Dozier MM, Heck JD, Gerhart JM, Rajendran N, David RM, Brennecke LH, Morrissey R. Toxicologic evaluation of flavor ingredients added to cigarette tobacco: 13 week inhalation exposures in rats. Inhal. Toxicol. 1998; 10:357-381

Gaworski CL, Heck JD, Bennett MB, Wenk ML. Toxicologic evaluation of flavor ingredients added to cigarette tobacco: skin painting bioassay of cigarette smoke condensate in SENCAR mice. Toxicology. 1999; 139(1-2):1-17.

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Tobacco Product Related Chemical and Biological Studies for Ingredients Tested Singly

References
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Toxicological Data on the Unburnt Ingredient

Organism	Test Type	Route	Reported Dose	Reference
mouse	LD ₅₀	<i>i.p.</i>	0.8 mg/kg	International Journal of Crude Drug Research. Vol. 23, Pg. 119, 1985
mouse	LD ₅₀	<i>i.v.</i>	239 mg/kg	Chinese Medical Journal Vol. 4, Pg. 319, 1978
rat	LD ₅₀	oral	1910 mg/kg	Drug and Chemical Toxicology. Vol. 3, Pg. 249, 1980

References

Chinese Medical Journal Vol. 4, Pg. 319, 1978

Drug and Chemical Toxicology. Vol. 3, Pg. 249, 1980

International Journal of Crude Drug Research. Vol. 23, Pg. 119, 1985