

Hexanal

Botanical Source

Synonyms	HEXYL ALDEHYDE,n-hexanal
IUPAC Name	Hexanal
CAS Reference	66-25-1
E Number	

Food Legislation

Council of Europe (CoE)	
Number	Comment
96	Listed by the Council of Europe as acceptable for use in food at up to 10 ppm.

US Food and Drug Administration	
Number	Comment
172.515	Approved by the US FDA. FDA 21 CFR 172.515

Joint FAO/WHO Expert Committee on Food Additives (JECFA)		
Number	ADI	Comment
92	No Safety concern @ intake	No safety concern at current levels of intake when used as a flavouring agent.

FEMA	
FEMA No.	Comment
2557	

Natural Occurrence and Use in Food
Found in apples, bananas, beef, bilberries, apricot, artichoke, asparagus, avocado, barley, beer, blackberry, blueberry, others; used in frozen dairy goods, baked goods, meat.

Estimated Intake From Food and Drink	
Daily Intake mg/kg/day	FEMA Possible Average Daily
10	0.351

Tobacco Legislation

Tobacco				
Country	Cigarettes	RYO	Cigars	Pipe
Afghanistan				
Algeria				
Argentina				
Australia				
Bahrain				
Brazil				
Burundi				
Canada				
Comoros				
Djibouti				
EEC				
Egypt				
Eritrea				
EU TPD2				
Fiji				
France	Y	Y	Y	Y
GCC (Bahrain,				
Germany	Y	Y	Y	Y
Hong Kong				
Hungary	Y	Y	Y	Y
Iceland				
Iran				
Iraq				
Jordan				
Kazakhstan				
Kuwait				
Libya				
Macedonia				
Madagascar				
Malaysia				

Maldives				
Mexico				
Moldova				
Montenegro				
New Zealand				
Nigeria				
Norway				
Pakistan				
Palestine				
Papua New Guinea				
Rwanda				
Samoa				
Saudi Arabia				
Serbia				
Solomon Island				
Somalia				
Somaliland				
South Sudan				
Sri Lanka				
Sweden				
Switzerland	Y	Y	Y	Y
Syria				
Tunisia				
Turkey				
UK				
United Arab				
Vietnam				

Y=Permitted for use in tobacco products. If use is limited, the maximum permitted level is given.

Tobacco Product related Chemical and Biological Studies

Smoke Chemistry		
Published Source	Level Tested %	Comment
Philip Morris	0.00010	An overall assessment of the data suggests that this ingredient did not add to the toxicity of smoke.
BAT	0.00100	At maximum application level this ingredient is not associated with significant increases in levels of Hoffmann analytes in smoke.

Ames Activity		
Published Source	Level Tested %	Comment
BAT	0.00100	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	0.00100	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	0.00100	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
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

Species	Test Conditions	End Point	Results	Reference
Human.	Volunteers (21-28 years old) were exposed for 2-hour periods to three different atmospheric hexanal concentrations on three separate occasions (exposures were at least 2 weeks apart). Participants graded their symptoms before during and after exposures by markings on 10-cm visual analogue scales for each symptom group (nose discomfort: burning, irritated or runny nose; throat or airway discomfort; breathing difficulty; solvent smell). 0, 2, 10 ppm [0, 8, 41 mg/m ³].	Respiratory irritation.	NOAEC 2 ppm [8 mg/m ³]. At 10 ppm subjects reported solvent smell –“somewhat”, and “other symptoms”. The investigators concluded that 10 ppm hexanal had a weak irritating effect. [See also LOCAL EFFECTS, Eye irritation section and GENERAL SYSTEMIC EFFECTS, single exposure, inhalation section.]	National Institute for Working Life, 2006; Ernstgård et al, 2006
Rabbit.	Dermal application of 10 mg hexanal to rabbits for 24 hours.	Skin irritation.	Mild irritation.	RIVM, 2006
Rabbit.	“Standard Draize test”; 500 mg applied to the skin for 24 hours.	Skin irritation.	Mild reaction.	RTECS, 2012
Rabbit.	Open irritation test”; 14.2 mg applied to the skin for 24 hours.	Skin irritation.	Mild reaction.	RTECS, 2012

Species	Test Conditions	End Point	Results	Reference
Human.	Volunteers (21-28 years old) were exposed for 2-hour periods to three different atmospheric hexanal concentrations (exposures were at least 2 weeks apart). Participants graded their symptoms before during and after exposures by markings on 10-cm visual analogue scales for each symptom group (eye discomfort: burning; irritating or running eyes). Blinking frequency was also measured. 0, 2, 10 ppm [8, 41 mg/m ³].	Eye irritation.	NOAEC 8 mg/m ³ . At 10 ppm subjects reported, eye discomfort, increased blinking frequency and “other symptoms”. The investigators concluded that 10 ppm hexanal had a weak irritating effect. [See also LOCAL EFFECTS, Respiratory irritation section and GENERAL SYSTEMIC EFFECTS, single exposure, inhalation section].	National Institute for Working Life, 2006; Ernstgård et al, 2006
Rabbit.	Application of 100 mg hexanal to rabbit eyes.	Eye irritation.	Mild irritation.	RIVM, 2006
Rabbit.	Standard Draize test”; application of 500 mg hexanal to rabbit eyes.	Eye irritation.	Mild irritation.	RTECS, 2012
Human.	Maximization test. Repeated covered skin applications of hexanal in petrolatum to 25 volunteers.	Skin sensitization.	No allergic reactions.	Opdyke, 1973

Species	Test Conditions	End Point	Results	Reference
Not specified.	Local lymph node assay (LLNA).	Skin sensitization.	EC3 45% making it an “extremely weak sensitizer”. (EC3 is the effective concentration for a SI (stimulation index) of 3 in proliferation of lymph node cells, a chemical is classified as a sensitizer if at one or more test concentrations it induces a three-fold or greater increase in draining lymph node cell proliferation). [This study explains evaluation of QSAR model in which LLNA data was generated to support development. Details of the LLNA study are not given; only EC3 value is reported.]	Patlewicz et al, 2004
Human.	Volunteers (21-28 years old) were exposed for 2-hour periods to three different atmospheric hexanal concentrations (exposures were at least 2 weeks apart). Participants graded their symptoms before during and after exposures by markings on 10-cm visual analogue scales for each symptom group (headache; fatigue; nausea; dizziness; feeling of intoxication). Lung function and inflammation markers (CRP and IL-6) in blood samples (taken 3 hours after the end of exposure) were also measured. 0, 2, 10 ppm [0, 8, 41 mg/m ³].	Pulmonary function.	No effects on pulmonary function or plasma inflammatory markers were noted. See also LOCAL EFFECTS, Eye irritation and Respiratory irritation sections].	National Institute for Working Life, 2006; Ernstgård et al, 2006

Species	Test Conditions	End Point	Results	Reference
Human.	Exposure of subjects for 30 seconds, 3 minutes or an unspecified duration to an atmosphere containing hexanal. 100, 1000 or 3000 mg/m ³ .	Not specified.	The highest concentration, caused cough, headache and eye watering in a number of subjects. Of these effects, only eye irritation was noted following a 30-second exposure to an atmosphere containing 1000 mg/m ³ or a 3-minute exposure to an atmosphere containing 100 mg/m ³ .	RTECS, 2012
Rat.	6 rats were exposed to a specified hexanal concentration for 4 hours or an unspecified concentration for 1 hour 2000 ppm [8200 mg/m ³] or "concentrated vapour"..	Mortality.	No deaths occurred after exposure to "concentrated vapour" for 1 hour, one death occurred after exposure to 8200 mg/m ³ for 4 hours.	HSDB, 2009
Mouse, Swiss-Webster or B6C3F ₁ .	Not specified.	Respiratory effects.	RD ₅₀ 1116 ppm [4575 mg/m ³] for B6C3F ₁ mice. RD ₅₀ 1029 ppm [4219 mg/m ³] for Swiss-Webster mice. RD ₅₀ is defined as the concentration that reduces respiratory rate by 50%.	National Institute for Working Life, 2006
Mammal.	Not specified.	Mortality, clinical signs of toxicity.	Lowest published toxic concentration, TCLo" 20,000 mg/m ³ ., associated with cough and conjunctival irritation.	RTECS, 2012
Mammal.	Not specified.	Mortality.	LD ₅₀ 3700 mg/kg bw.	RTECS, 2012

Species	Test Conditions	End Point	Results	Reference
Mouse.	Not specified.	Mortality, clinical signs of toxicity.	LD ₅₀ 8292 mg/kg bw, associated with behavioural somnolence (general depressed activity), dyspnea.	RTECS, 2012
Rat.	Not specified.	Mortality.	4890 mg/kg bw.	National Institute for Working Life, 2006
Rat.	Males given a single oral gavage administration.	Mortality.	7740 mg/kg bw.	JECFA, 1998
Mammalian.	Repeated exposure to a number of animals for 2 hours/day for 30 days, to an atmosphere containing hexanal. 750 mg/m ³ .	Mortality.	Deaths occurred.	RTECS, 2012

Species	Test Conditions	End Point	Results	Reference
Rat, Sprague-Dawley.	10 rats per sex and dose were administered hexanal in drinking water (0.5% w/v Emulphor was added to solubilize hexanal) for 28 days. Two control groups (water only and water with 0.5% w/v Emulphor) were used. 0, 1, 10, 100 or 1000 mg/litre in drinking water, providing 0, 0.1, 1.2, 12.6, 124.7 mg/kg bw/day (males) 0, 0.1, 0.9, 8.6, 95.7 mg/kg bw/day (females)	Overt signs of toxicity, body weight, food and water intake, haematological and clinical chemistry parameters, gross and histological examination of a wide range of tissues and organs, some organ weights.	NOAEL 124.7 mg/kg bw/day (males) (highest dose tested). NOAEL 96 mg/kg bw/day (females) (highest dose tested). "No overt toxic effects. Although treatment-related morphological changes were observed in the highest dose groups; these were considered to be mild and adaptive in nature, and could not be related to any functional changes".	Komsta et al, 1988
Rat, F-344.	3 Male rats received hexanal in the diet for 3 weeks, 13 control animals received an equivalent unsupplemented diet. Blood samples from the abdominal aorta were taken for determination of triglyceride and cholesterol levels. 2% v/w [about 828 mg/kg bw/day].	Serum lipid content.	Serum and cholesterol levels were statistically significantly reduced.	Moody & Reddy, 1982
Rat, F-344.	4 Male rats received hexanal in the diet for 3 weeks, 13 control animals received an equivalent unsupplemented diet. Electron microscopic examination of liver sections; measurement of hepatic catalase and carnitine acetyltransferase.	Body weight, liver weight, liver enzymes, peroxisome proliferation.	Statistically significant reduction in body weight gain; statistically significant increase in the activities of catalase and carnitine acetyltransferase in the liver; some evidence of peroxisome proliferation (ratio of mitochondria:peroxisomes 5:2 in treated animals, 5:1 in controls).	Moody & Reddy, 1978

Species	Test Conditions	End Point	Results	Reference
Human hepatocytes; Rat hepatocytes.	Cells exposed for up to 20 hours to hexanal and examined for evidence of unscheduled DNA synthesis (UDS). 3 - 30 mM [0.3 - 3 mg/ml].	DNA damage.	-ve (human hepatocytes). +ve at 3 mg/ml (rat hepatocytes) although at this concentration half the cells died. Investigators concluded that hexanal is "at most weakly genotoxic" and that the probability of genotoxic effects on humans "negligible".	Martelli et al, 1994; Martelli, 1997; National Institute for Working Life, 2006
Human, A549 lung cells.	Cells were exposed to gas phase containing hexanal for 1 hour after which cytotoxicity and genotoxicity were determined using erythrosine B staining and a comet assay respectively. 2, 100, 1000 and 2000 mg/m ³ .	DNA damage	Cytotoxic at 2000 mg/m ³ . No DNA damage at any exposure concentration.	Gminski et al, 2010
Human HL60 (promyelocytic leukaemia) cells	Assay to detect DNA-protein crosslinks. Incubation for 4 hours; post-treatment +/- the reducing agent sodium borohydride. 40 mM [4 mg/ml].	DNA-protein crosslinking.	-ve.	Schoenfield and Witz, 2000
Chinese hamster (V79) lung cells	Mammalian cell gene mutation assay without metabolic activation. Resistance development to 6-thioguanine or ouabain was evaluated as a measure of genotoxicity. 3 - 30 mM. [0.3 - 3 mg/ml].	Mutation.	+ve.	Brambilla et al, 1989; National Institute for Working Life, 2006
Chinese hamster ovary (K1) cells.	Without metabolic activation. Treated with hexanal for 90 minutes and evaluated for single strand breaks and alkali-labile sites. 0.5, 1.5, 4.5 mM [0.05, 0.15, 0.45 mg/ml].	DNA damage.	+ve for strand breaks. -ve for cross-links.	Marinari et al, 1984; EPA, 2008

Species	Test Conditions	End Point	Results	Reference
<i>Salmonella typhimurium</i> , strains TA98, TA100, TA104 and <i>Escherichia coli</i> , strain WP2uvrA/pKM101	Bacterial reverse mutation (Ames) assay with and without S9, pre-incubated at 37 °C for 20 minutes.	Mutation.	-ve.	Kato et al, 1989
<i>Salmonella typhimurium</i> , strains TA102, TA104.	Bacterial reverse mutation (Ames) assay without S9. Pre-incubation; revertants scored after 48 hours. Up to 1 mg/plate.	Mutation.	-ve. Maximum non-toxic dose 8 µM [presumably 0.8 mg/plate].	Marnett et al, 1985
<i>Salmonella typhimurium</i> , strains TA98, TA100, TA1535, TA1537.	Bacterial reverse mutation (Ames) assay, spot test, without S9. 3 µmol/plate [0.3 mg/plate].	Mutation.	-ve.	Florin et al, 1980
<i>Salmonella typhimurium</i> , strain TA1531.	Bacterial reverse mutation (Ames) assay with S9.	Mutation.	+ve (weak)	RIVM, 2006

Species	Test Conditions	End Point	Results	Reference
<i>Salmonella typhimurium</i> , strain TA100.	Bacterial reverse mutation (Ames) assay performed twice using the plate incorporation method and the pre-incubation protocol. Metabolic activation was not used. Experiments were performed in triplicate with positive controls. 0, 0.00003, 0.0001, 0.0003, 0.001, 0.003, 0.01, 0.03 mmol/plate [0, 0.003, 0.01, 0.03, 0.1, 0.3, 1.0 and 3.0 mg/plate].	Mutation.	-ve. Toxic at 1 mg/plate and above.	Benigni et al, 2005

References

Benigni, R., Conti, L., Crebelli, R., Rodomonte, A., Vari, M.R., 2005 Simple and α,β -unsaturated aldehydes: correct prediction of genotoxic activity through structure-activity relationship models. *Envir. molec. Mutagen.*, 46, 268-280.

Brambilla, G., Cajelli, E., Canonero, R., Martelli, A., Marinari, U.M., 1989 Mutagenicity in V79 Chinese hamster cells of *n*-alkanals produced by lipid peroxidation. *Mutagenesis*, 4, 277-279.

ECHA

European Chemicals Agency. Information on Chemicals. Accessed April 2013. Available at: <http://echa.europa.eu/information-on-chemicals>.

EPA, 2008

US Environmental Protection Agency. Toxicological review of propionaldehyde (CAS No. 123-38-6) in support of summary information on the Integrated Risk Information System (IRIS). Available at: <http://www.epa.gov/iris/toxreviews/1011tr.pdf>
EPA/635/R-08/003F

Ernstgård, L., Iregren, A., Sjögren, B., Svedberg, U., Johanson, G., 2006

Acute effects of exposure to hexanal vapors in humans. *J. occup. envir. Med.*, 48, 573-580.

Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980

Screening of tobacco smoke constituents for mutagenicity using the Ames' test. *Toxicology*, 15, 219-232.

Gaworski, C.L., Dozier, M.M., Heck, J.D., Gerhart, J.M., Rajendran, N., David, R.M., Brennecke, L.H., Morrissey, R., Bennett, M.B., 1998 Toxicologic evaluation of flavour ingredients added to cigarette tobacco: 13 week inhalation exposure in rats. *Inhalation Toxicology*, 10, 357-381.

Gminski, R., Tang, T., Mersch-Sundermann, V., 2010 Cytotoxicity and genotoxicity in human lung epithelial A549 cells caused by airborne volatile organic compounds emitted from pine wood and oriented strand boards. *Toxicology Lett.*, 196, 33-41.

HSDB, 2009

Hazardous Substances Data Bank. Last revision date 17 August 2009. Available at: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>

JECFA, 1998

Safety evaluation of certain food additives and contaminants. Prepared by the forty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives. *WHO Fd Add. Ser.*, 40. Available at: <http://www.inchem.org/documents/jecfa/jecmono/v040je10.htm>

Kato, F., Araki, A., Nozaki, K., Matsushima, T., 1989 Mutagenicity of aldehydes and diketones. *Mutation Res.*, 216, 366-367.

Komsta, E., Chu, I., Secours, V.E., Valli, V.E., Villeneuve, D.C., 1988 Results of a short-term toxicity study for three organic chemicals found in Niagara river drinking water. *Bull. envir. Contam. Toxicol.*, 41, 515-522.

Marinari, U.M., Ferro, M., Sciaba, L., Finollo, R., Bassi, A.M., Brambilla, G., 1984 DNA-damaging activity of biotic and xenobiotic aldehydes in Chinese hamster ovary cells. *Cell Biochem. Func.*, 2, 243-248.

Marnett, L.J., Hurd, H.K., Hollstein, M.C., Levin, D.E., Esterbauer, H., Ames, B.N., 1985 Naturally occurring carbonyl compounds

Martelli, A., Canonero, R., Cavanna, M., Ceradelli, M., Marinari, U.M., 1994 Cytotoxic and genotoxic effects of five n-alkanals in primary cultures of rat and human hepatocytes. *Mutation Res.*, 323, 121-126.

Martelli, A., 1997

Primary human and rat hepatocytes in genotoxicity assessment. *In Vivo*, 11, 189-193.

Moody, D.E. and Reddy, J.K., 1978 Hepatic peroxisome (microbody) proliferation in rats fed plasticizers and related compounds. *Toxic. appl. Pharmac.*, 45, 497-504.

Moody, D.E. and Reddy, J.K., 1982 Serum triglyceride and cholesterol contents in male rats receiving diets containing plasticizers and analogues of the ester 2-ethylhexanol. *Toxicology Lett.*, 10, 379-383.

National Institute for Working Life, 2006

Consensus report for n-hexanal. Scientific Basis for Swedish Occupational Standards XXVII. Ed. Johan Montelius. Criteria Group for Occupational Standards National Institute for Working Life S-113 91 Stockholm, Sweden. pp.31-41. *Arbete och Halsa*, NR 2006:11. Available at: http://www.inchem.org/documents/kemi/kemi/ah2006_11.pdf

Opdyke DLJ (1973).

Monographs on Fragrance Raw Materials: Aldehyde C-6. *Fd Cosmet. Toxicol.*, 11, 111.

Patlewicz, G.Y., Basketter, D.A., Pease, C.K., Wilson, K., Wright, Z.M., Roberts, D.W., Bernard, G., Arnau, E.G., Lepoittevin, J.P., 2004 Further evaluation of quantitative structure-activity relationship models for the prediction of the skin sensitization potency of selected fragrance allergens. *Contact Dermatitis*, 50, 91.

RIVM, 2006 Dutch National Institute for Public Health and the Environment (RIVM) report 340630002/2006. I. van Andel et al, Adverse health effects of cigarette smoke: aldehydes – crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde. Available at: <http://www.rivm.nl/bibliotheek/rapporten/340630002.pdf>

RTECS, 2012 Registry of Toxic Effects of Chemical Substances. Record for Hexanal (66-25-1). Last updated April 2012.

Schoenfeld, H.A. and Witz, G., 2000

Structure-activity relationships in the induction of DNA-protein cross-links by hematotoxic ring-opened benzene metabolites and related compounds in HL60 cells. *Toxicology Lett.*, 116, 79-88.