

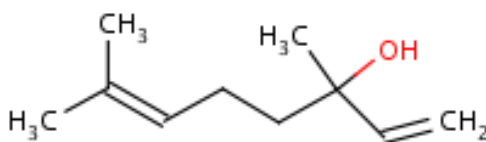
Additive Toxicity Statement

Linalool



DESCRIPTION

Name	Linalool
IUPAC name	3,7-dimethylocta-1,6-dien-3-ol
CAS no	78-70-6
EINECS no.	201-134-4
Molecular formula	C ₁₀ H ₁₈ O
Structural formula	



Molecular weight (g/mol.) 154.25

CLP HEALTH HAZARD CLASSIFICATION

This ingredient has been classified under Regulation (EC) No 1272/2008 of the European Parliament and of the Council and is in the classification and labelling inventory.

The CLP classifications of this ingredient are not considered applicable for one, or more, of the following reasons:

- the level required to elicit a response in a toxicological study, with a relevant route of exposure, is far higher than that of its use in BAT products
- the toxicological effect identified does not relate to the route of exposure associated with its use in BAT products
- no relevant toxicological study was identified relating to the route of exposure, and there is only limited consumer exposure to this ingredient associated with its use in BAT products

AVAILABLE STUDIES

The available toxicity studies indicated in the Commission Implementing Decision (EU) 2015/2186 have been provided as a bibliography of published papers. The studies were obtained by BAT for toxicological assessments, to ensure that additives do not increase the inherent risk associated with the use of our products.

The risk assessment starts with a comprehensive search for relevant papers, using the additive's name, major synonyms and CAS Registry Number. The main sources searched are: TRACE¹, Toxnet², RTECS³, TSCATS⁴, INCHEM⁵, Europa Food Flavouring⁶, ECHA⁷, EAFUS⁸, ChemIDplus⁹ and eChemportal¹⁰.

RISK ASSESSMENT

Toxicological assessments are carried out by our scientists (including a number of European Registered Toxicologists (ERT)) at our Research and Development facilities in the UK. Our approach excludes the use of formally classified genotoxicants, non-threshold carcinogens, mutagens, reproductive and developmental toxicants as additives. Based on Levels of Concern and weight-of evidence, our approach ensures that additives are used at levels lower than the relevant toxicological reference value.

Following a comprehensive search for all available toxicological information, our toxicologists select the most appropriate studies for evaluation for the intended route of exposure. To do this, our toxicologists evaluate the quality of all pertinent studies identified and the data used. The evaluation of data quality includes an assessment of its relevance and reliability as well as the adequacy of the information for hazard/risk assessment purposes, following the principles described by Klimisch *et al*¹¹.

In the majority of BAT's products, a number of the additives are heated or combusted. The effects of heating or combustion on additive toxicity, have been addressed by extensive testing. The results of pyrolysis, smoke chemistry, *in vitro* cytotoxicity, *in vitro* genotoxicity, inhalation toxicity and tumourigenicity studies have been widely published in peer-reviewed journals. These studies are included in our risk assessments where applicable by product class.

Examples of our assessment processes can be found in published literature for example:

- An overview of the effects of tobacco ingredients on smoke chemistry and toxicity¹²
- An approach to ingredient screening and toxicological risk assessment of flavours in e-liquids¹³
- Contact sensitisation risk assessment approach for pouched snus ingredients¹⁴
- Assessment of the irritation potential of Swedish snus ingredients using the Epioral™ tissue model¹⁵

Further examples of our scientific publications are available at www.bat-science.com.

Health risks of tobacco use have primarily been determined in long term human epidemiological studies. For example, the smoking population in countries such as Canada, Australia and the UK have historically smoked Virginia style cigarettes, which contain few additives. In other countries such as the US and Germany smokers prefer American-blended style cigarettes, which contain significantly more additives. Notwithstanding the distinction in historical use of additives in these countries, there appears to be no obvious difference in the relative risks of cigarette smoking for these types of cigarette, or on the incidence of diseases such as lung cancer and chronic obstructive pulmonary disease¹⁶, suggesting that the addition of additives to cigarettes may not increase the incidence of diseases associated with smoking.

ADDICTIVENESS

In its 2010 opinion on Addictiveness and Attractiveness of additives¹⁷, SCENIHR came to the clear conclusion that no additive could be identified which has an "addictive" effect in isolation, and that there are no indications that additives increase the "addictive" effect of nicotine itself.

In a more recent final opinion¹⁸, SCENIHR reviewed 1260 additives and selected only 14 substances for further study because of their contribution to addictiveness to smoking.

CONCLUSION

Based on the available scientific evidence, BAT's scientists have concluded that the additives used in BAT's tobacco products, do not add to the toxicological risks of using those products.

1. Available at: [http://www.bibra-information.co.uk/supported access to our chemical toxicology database TRACE.html](http://www.bibra-information.co.uk/supported%20access%20to%20our%20chemical%20toxicology%20database%20TRACE.html)
2. Available at: <http://toxnet.nlm.nih.gov/index.html>
3. Available at: <http://ccinfoweb.ccohs.ca/rtecs/search.html>
4. Available at: <http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384>
5. Available at: <http://www.inchem.org/>
6. Available at: http://ec.europa.eu/food/food/chemicalsafety/flavouring/database/dsp_search.cfm
7. Available at: <http://echa.europa.eu/information-on-chemicals>
8. Available at: <http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=eafusListing>
9. Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp>
10. Available at: http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en
11. Klimisch, H.J., Andreae, E., Tillmann, U., (1997). A systematic approach for evaluating the quality of experimental and ecotoxicological data. *Regul. Toxicol. Pharmacol.* 25, 1–5.
12. R. R. Baker, E. D. Massey and G. Smith. An overview of the effects of tobacco ingredients on smoke chemistry and toxicity. *Food Chem. Toxicol.* 42 Suppl: S53-S83, 2004.
13. S. Costigan and C. Meredith. An approach to ingredient screening and toxicological risk assessment of flavours in e-liquids. *Regul. Toxicol. Pharmacol.* 72 (2):361-369, 2015.
14. B. Lang, S. Costigan, S. Goodall and C. Meredith. Contact sensitisation risk assessment approach for pouched snus ingredients. *Toxicology Letters* 229S:S109, 2014. (Abstract)
15. L. Neilson, S. Faux, S., Hinchcliffe, T. Jai and C. Meredith. Assessment of the irritation potential of swedish snus ingredients using the epioral™ tissue model. Society of Toxicology, Baltimore, USA, March 15-19th. *The Toxicologist*, Volume 108, no 1, pg 307-308 (March 2009) (Conference Poster)
16. World Health Organisation, 2004. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Volume 83. Tobacco smoke and involuntary smoking. p 171. International Agency for Research on Cancer (IARC), Lyon, 2004
17. SCENIHR, 2010. Addictiveness and Attractiveness of Tobacco Additives. The Scientific Committee on Emerging and Newly Identified Health Risks. ISBN 978-92-79-12788-5. European Union. Available at: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_029.pdf.
18. SCENIHR, 2015. Final Opinion on Additives used in Tobacco Products (Opinion 1). The Scientific Committee on Emerging and Newly Identified Health Risks. European Union. Available at: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_051.pdf.

REFERENCES

Acros Organics, 2008

Acros Organics N.V. Material safety data sheet: linalool. 8 May 2008. Acros Organics N.V., One Reagent Lane, Fair Lawn, NJ 07410. Available at: <https://fscimage.fishersci.com/msds/21702.htm>.

Berić, T., Nikolić, B., Stanojević, J., Vuković-Gacić, B., Knezević-Vukcević, J., 2008

Protective effect of basil (*Ocimum basilicum* L.) against oxidative DNA damage and mutagenesis. *Fd Chem. Toxic.*, 46, 724-732.

Bickers, D., Calow, P., Greim, H., Hanifin, J.M., Rogers, A.E., Saurat, J.H., Sipes, I.G., Smith, R.L., Tagami, H., 2003

A toxicologic and dermatologic assessment of linalool and related esters when used as fragrance ingredients. *Fd Chem. Toxic.*, 41, 919-942.

Burdock, G.A., 2010

Fenaroli's Handbook of Flavor Ingredients. 6th Edition. CRC Press, Boca Raton. ISBN 978-1-4200-9077-2.

CCRIS, 2010

Chemical Carcinogenesis Research Information System. Record for linalool. Last revision date 2 June 2010. Available at: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS>

ChemIDplus

Accessed: March 2013. Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>

CoE, 2000

Chemically-defined flavouring substances. Council of Europe Publishing. ISBN 92-871-4453-2.

Di Sotto, A., Evandri, M.G., Mazzanti, G., 2008

Antimutagenic and mutagenic activities of some terpenes in the bacterial reverse mutation assay. *Mutation Res.*, 653, 130-133.

Di Sotto, A., Mazzanti, G., Carbone, F., Hrelia, P., Maffei, F., 2011

Genotoxicity of lavender oil, linalyl acetate, and linalool on human lymphocytes *in vitro*. *Envir. molec. Mutagen.*, 52, 69-71.

EC, 2002

European Commission decision of 23 January 2002 amending Commission Decision 1999/217/EC as regards the register of flavouring substances used in or on foodstuffs (notified under document number C(2002) 88) (2002/113/EC). Official Journal of the European Communities 20.2.2002, L 49/1. Available at: http://ec.europa.eu/food/fs/sfp/addit_flavor/flav17_en.pdf.

ECHA

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

EFSA, 2011

Additive Toxicity Statement

Linalool



European Food Safety Authority. Scientific Opinion on Flavouring Group Evaluation 18, Revision 2 (FGE.18Rev2): Aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters from chemical groups 6 and 8.1. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids. *EFSA J.*, 9(5), 1847. Available at: <http://www.efsa.europa.eu/en/search/doc/1847.pdf>

EPA

US Environmental Protection Agency. Integrated Risk Information System (IRIS). Accessed December 2014. Available at: http://www.epa.gov/iris/search_human.htm and http://cfpub.epa.gov/ncea/iris_drafts/erd.cfm?excCol=Archive&archiveStatus=both

FDA, 2011

US Food and Drug Administration. Everything added to Food in the United States (EAFUS). Last updated 14 November 2011. Available at: <http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=eafusListing>

FFHPVC, 2001

The Flavor and Fragrance High Production Volume Consortia. The Terpene Consortium. Test plan for terpenoid tertiary alcohols and related esters. Available at: <http://www.epa.gov/hpv/pubs/summaries/tertestr/c12930tp.pdf>.

GESTIS

Gefahrstoffinformationssystem (Databases on hazardous substances). Accessed March 2013. Available at: http://limitvalue.ifa.dguv.de/Webform_gw.aspx

Gould, M.N., Maltzman, T., Tanner, M., Boston, J., Hurt, L., Elson, C., 1987

Anticarcinogenic effects of terpenoids in orange peel. Proceedings of the 78th Annual Meeting of the American Association for Cancer Research 28, 153.

HSDB, 2009

Hazardous Substances Data Bank. Record for linalool. Last Revision Date: 5 January 2009. Available at: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>

IARC

International Agency for Research on Cancer. World Health Organization. Accessed March 2013. Available at: <http://www.iarc.fr/>

ICSC, 1997

International Chemical Safety Card no. 0912; linalool. Prepared in the context of cooperation between the International Programme on Chemical Safety and the Commission of the European Communities. Available at: <http://www.inchem.org/documents/icsc/icsc/eics0912.htm>.

Ishidate, M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984

Primary mutagenicity screening of food additives currently used in Japan. *Fd Chem. Toxic.*, 22, 623-636.

JECFA, 1999

Additive Toxicity Statement

Linalool



Safety evaluation of certain food additives. Prepared by the 51st meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additive Series 42. World Health Organization, Geneva. Available at: <http://www.inchem.org/documents/jecfa/jecmono/v042je17.htm>.

JRC

Joint Research Centre. European chemical Substances Information System (ESIS). Accessed March 2013. Available at: <http://esis.jrc.ec.europa.eu/>

Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003
Fragrance material review on linalool. *Fd Chem. Toxic.*, 41, 943-964.

Letizia, C., Api, A., Politano, V.T., Lewis, E.M., Hoberman, A.M., Christian, M., Diener, R.M., 2007
Evaluation of the developmental toxicity of linalool in rats. *Toxicologist*, 96 (Suppl. 1), 92. Abstract 441.

Linck V. de M., da Silva, A.L., Figueiró, M., Piato, A.L., Herrmann, A.P., Dupont Birck, F., Caramão, E.B., Nunes, D.S., Moreno, P.R., Elisabetsky, E., 2009
Inhaled linalool-induced sedation in mice. *Phytomedicine*, 16(4), 303-307.

NTP

US National Toxicology Program. Accessed December 2014. Available at: <http://www.niehs.nih.gov/research/resources/databases/cebs/index.cfm> and <http://tools.niehs.nih.gov/cebs3/ui/>

NTP, 1999

National Toxicology Program. Salmonella: study summary. Study ID A67784. Available at: http://tools.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=salmonella.overallresults&cas_no=78-70-6&endpointlist=SA.

Oda, Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1978
Mutagenicity of food flavours in bacteria (1st report). *Osaka Furitsu KEKHESEH*, 9, 177-181 (in Japanese, some data given in English).

OECD, 2002

Organisation for Economic Co-operation and Development. Screening information dataset (SIDS) on linalool (CAS 78-70-6). SIAR for SIAM 14. Available at: <http://www.chem.unep.ch/irptc/sids/OECD/SIDS/78706.pdf>.

Politano, V.T., Lewis, E.M., Hoberman, A.M., Christian, M.S., Diener, R.M., 2008
Evaluation of the developmental toxicity of linalool in rats. *Int. J. Toxic.*, 27, 183-188.

Roe, F.I.C. and Field, W.E.H., 1965

Chronic toxicity of essential oils and certain other products of natural origin. *Fd Chem. Toxic.*, 3, 311-324.

Russin, W.A., Hoesly, J.D., Elson, C.E., Tanner, M.A., Gould, M.N., 1989

Inhibition of rat mammary carcinogenesis by monoterpenoids. *Carcinogenesis*, 10, 2161-2164.

SCENIHR, 2010

Addictiveness and Attractiveness of Tobacco Additives. The Scientific Committee on Emerging and Newly Identified Health Risks. ISBN 978-92-79-12788-5. European Union. Available at: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenih_r_o_029.pdf

Shen, J., Nijima, A., Tanida, M., Horii, Y., Maeda, K., Nagai, K., 2005

Olfactory stimulation with scent of lavender oil affects autonomic nerves, lipolysis and appetite in rats. *Neuroscience Lett.*, 383, 188-193.

SRC, 2013

Syracuse Research Corporation. Interactive PhysProp Database Demo. Record for linalool. Available at: <http://www.syrres.com/what-we-do/databaseforms.aspx?id=386>

Stoner, G.D., Shimkin, M.B., Kniazeff, A.J., Weisburger, J.H., Weisburger, E.K., Gori, G.B., 1973

Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumour response in strain A mice. *Cancer Res.*, 33, 3069-3085.

ToxTree

Estimation of toxic hazard – a decision tree approach. Version 2.6.13. IdeaConsult Ltd. Available at: <http://toxtree.sourceforge.net>.

Wattenberg, L.W., 1991

Inhibition of azoxymethane-induced neoplasia of the large bowel by 3-hydroxy-3,7,11-trimethyl-1,6,10-dodecatriene (nerolidol). *Carcinogenesis*, 12, 151-152.

Willis, D.N. and Morris, J.B., 2013

Modulation of sensory irritation responsiveness by adenosine and malodorants. *Chem. Senses*, 38, 91-100.

Yoo, Y.S., 1986

Mutagenic and antimutagenic activities of flavouring agents used in foodstuffs. *J. Osaka Cy med. Cent.*, 34, 267-288.