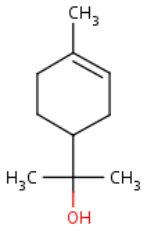
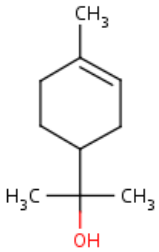
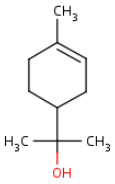
Additive Toxicity Statement

Terpineol (alpha-)

DESCRIPTION

Name	Terpineol (alpha-)
IUPAC name CAS 98-55-5 CAS 10482-56-1 CAS 8000-41-7	 2-(4-methyl-1-cyclohex-3-enyl)propan-2-ol 2-(1S)-4-methyl-1-cyclohex-3-enyl]propan-2-ol 2-(4-methyl-1-cyclohex-3-enyl)propan-2-ol
CAS no	98-55-5; 10482-56-1; 8000-41-7
EINECS no CAS 98-55-5 CAS 10482-56-1 CAS 8000-41-7	 202-680-6;219-448-5 233-986-8 232-268-1
Molecular formula	$C_{10}H_{18}O$
Structural formula CAS 98-55-5	 non-stereospecific
CAS 10482-56-1	 *S*- (or *l*-) isomer
CAS 8000-41-7	 Mixed regioisomers; alpha – terpineol, the major constituent, shown here.

Molecular weight (g/mol) 154.251

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: TRACE[1], Toxnet[2], RTECS[3], TSCATS[4], INCHEM[5], Europa Food Flavouring[6], ECHA[7], EAFUS[8], ChemIDplus[9] and eChemportal[10].

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 toxicity[12]
- An approach to ingredient screening and toxicological risk assessment of flavours in e-liquids[13]
- Contact sensitisation risk assessment approach for pouched snus ingredients[14]
- Assessment of the irritation potential of Swedish snus ingredients using the Epioral™ tissue model[15]

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 disease[16], 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 additives[17], 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 opinion[18], 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
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. at: http://echa.europa.eu/information-on-chemicals
7. Available at: http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=eafusListing
8. Available at: http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp
9. Available at: http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en
10. 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.
11. 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.
12. 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.
13. B. Lang, S. Costigan, S. Goodall and C. Meredith. Contact sensitisation risk assessment approach for pouched snus ingredients. Toxicology Available at: http://ec.europa.eu/food/food/chemicalsafety/flavouring/database/dsp_search.cfm
14. Available 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

Alfa Aesar
Accessed September 2013. Available at: http://www.alfa.com/en/go160w.pgm?srchtyp=product

Alfa Aesar, 2013
Material Safety Datasheet (MSDS) for Terpineol, mixed isomers (8000-41-7). Revision 27 June 2013.
Available at: http://www.alfa.com/content/msds/british/H60146.pdf

Alfa Aesar, 2011
Material Safety Datasheet (MSDS) for alpha-Terpineol (98-55-5). Revision 16 September 2011.
Available at: http://www.alfa.com/content/msds/british/16285.pdf

Bhatia, S.P., Letizia, C.S., Api, A.M., 2008a
Fragrance material review on alpha-terpineol. Fd Chem. Toxic., 46, S280-S285.

Bhatia, S.P., McGinty, D., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008b
Fragrance material review on terpineol (CAS 8000-41-7). Fd Chem. Toxic., 46, S275-S279.

Bhatia, S.P., Letizia, C.S., Api, A.M., 2008c
Fragrance material review on (-)-alpha-terpineol. Fd Chem. Toxic., 46, S204-S205.

Buchbauer, G., Jirovetz, L., Jäger, W., Plank, C., Dietrich, H., 1993
Fragrance compounds and essential oils with sedative effects upon inhalation. J. pharm. Sci., 82, 660-664.

Burdock, G.A., 2010
Fenaroli's Handbook of Flavor Ingredients. 6th Edition. CRC Press, Boca Raton. ISBN 978-1-4200-9077-2.

CCRIS
Chemical Carcinogenesis Research Information System. alpha-Terpineol. CCRIS no 3204. Last updated 28 March 2001. Available at: http://toxnet.nlm.nih.gov/cgi-bin/sis/search.

ChemIDplus (a)
Record for alpha-Terpineol (98-55-5). Accessed September 2013. Available at: http://chem.sis.nlm.nih.gov/chemidplus/

ChemIDplus (b)
Record for (L)-alpha-Terpineol (10482-56-1). Accessed September 2011. Available at: http://chem.sis.nlm.nih.gov/chemidplus/

ChemIDplus (c)
Record for Terpineol (8000-41-7). Accessed September 2011. Available at: http://chem.sis.nlm.nih.gov/chemidplus/

ChemSpider
Royal Society of Chemistry chemical structure database. Accessed September 2013. Available at: http://www.chemspider.com/

CoE, 2000
Chemically-defined flavouring substances. Council of Europe Publishing. ISBN 92-871-4453-2.

CoE, 1992
Flavouring substances and natural sources of flavourings. Volume I. 4th Edition. Chemically-defined flavouring substances. Council of Europe Publishing. ISBN 2-7160-0147-2.

CoE, 1981
Flavouring substances and natural sources of flavourings 3rd Edition. Maisonneuve. ISBN 27160-0081-6.

ECHA
European Chemicals Agency. Information on registered substances. Available at: http://apps.echa.europa.eu/registered/registered-sub.aspx

ECHA, 2013
European Chemicals Agency. Classification and Labelling (C&L) Inventory database. Last updated 03 August 2013. Available at: http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database

EFSA
European Food Safety Authority. Accessed September 2013. Available at: http://www.efsa.europa.eu/

EFSA, 2009
European Food Safety Authority. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission on Flavouring Group Evaluation 18, Revision 1 (FGE.18 Rev1): aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters from chemical groups 6 and 8. (EFSA-Q-2003-161B). (Adopted on 31 January 2008). EFSA J.,l 978, 1-85. Available at: http://www.efsa.europa.eu/cs/BlobServer/Scientific_Opinion/afc_ej978_fge18Rev1_op_en.pdf?sbinary=true

EPA
US Environmental Protection Agency. Integrated Risk Information System (IRIS). Accessed September 2013. Available at: http://www.epa.gov/iris/search_human.htm and http://cfpub.epa.gov/ncea/iris_drafts/erd.cfm?excCol=Archive&archiveStatus=both

EPI Suite
Accessed September 2013. The database is available to download at: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm

FDA, 2013
US Food and Drug Administration. Everything added to Food in the United States (EAFUS). Last updated 23 April 2013. Available at: http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=eafusListing

Fisher Scientific
Accessed September 2013. Available at: http://www.fisher.co.uk/index.php/en/technical-support

Fisher Scientific, 2010
Material Safety Datasheet for a-Terpineol (98-55-5). Revision date 29 January 2010. Available at: http://www.fisher.co.uk/index.php/en/technical-support

Flavis (a)
EUROPA food flavouring website. Record for alpha-Terpineol (98-55-5). Accessed September 2013. Available at: http://ec.europa.eu/food/food/chemicalsafety/flavouring/database/index.cfm

Flavis (b)
EUROPA food flavouring website. Record for Terpineol (8000-41-7). Accessed September 2013. Available at: http://ec.europa.eu/food/food/chemicalsafety/flavouring/database/index.cfm

Flavis (c)
EUROPA food flavouring website. Accessed September 2013. Available at: http://ec.europa.eu/food/food/chemicalsafety/flavouring/database/dsp_search.cfm

Friedrich, K., Delgado, I.F., Santos, L.M., Paumgartten, F.J., 2007
Assessment of sensitization potential of monoterpenes using the rat popliteal lymph node assay. Fd Chem. Toxic., 45, 1516-1522.

Frosch, P.J., Pilz, B., Andersen, K.E., Burrows, D., Camarasa, J.G., Dooms-Goossens, A., Ducombs, G., Fuchs, T., Hannuksela, M., Lachapelle, J.M., Lahti, A., Maibach, H.I., Menné, T., Rycroft, R.J.G., Shaw, S., Wahlberg, J.E., White, I.R., Wilkinson, J.D., 1995
Patch testing with fragrances: results of a multicenter study of the European Environmental and Contact Dermatitis Research Group with 48 frequently used constituents of perfumes. Contact Dermatitis, 33, 333-342.

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

GESTIS (b)
Record for Terpineol (8000-417). Accessed September 2013. Available at: http://gestis-en.itrust.de/nxt/gateway.dll/gestis_en/122876.xml?f=templates$fn=document-frameset.htm$q=%5Bfield,schnellsuche%3A8000z041z07%5D%20$x=server$3.0#LPHit1

Gomes-Carneiro, M.R., Felzenszwalb, I., Paumgartten, F.J., 1998
Mutagenicity testing of (+/-)-camphor, 1,8-cineole, citral, citronellal, (-)-menthol and terpineol with the Salmonella/microsome assay. Mutation Res., 416, 129-136.

Good Scents Company (a)
Record for alpha-terpineol (98-55-5). Accessed September 2013. Available at: http://www.thegoodscentscompany.com/data/rw1011252.html

Good Scents Company (b)
Record for (-)-alpha-terpineol (10482-56-1). Accessed September 2013. Available at: http://www.thegoodscentscompany.com/data/rw1218601.html

Good Scents Company (c)
Record for terpineols (unspec.) (mixed isomers) (8000-41-7). Accessed September 2013. Available at: http://www.thegoodscentscompany.com/data/rw1311481.html

Greif, N., 1967
Cutaneous safety of fragrance material as measured by the maximization test. Am. Perfumer Cosmet., 82, 54-57.

Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B., Curren, R.D., 1989
An evaluation of food flavoring ingredients in a genetic toxicity screening battery. Toxicologist 9, 257.

HSDB
Hazardous Substances Data Bank. Accessed September 2013. Available at: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

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

Ishihara, M., Itoh, H., Nishimura, M., Kinoshita, M., Kantoh, H., Nogami, T., Yamada, K., 1986
Closed epicutaneous test. Skin Res., 28, 230-240.

JECFA, 2000
Evaluation of certain food additives. WHO Tech.l Rep., 891. Fifty-first report of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization, Geneva. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_891.pdf.

JECFA
Joint Expert Committee on Food Additives. Monographs and Evaluations. Accessed September 2013. Available at: http://www.inchem.org/pages/jecfa.html

JECFA, 1999
Safety evaluation of certain food additives. Aliphatic acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances. WHO Fd Add. Ser., 42. Prepared by the fifty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization, Geneva. Available at: http://www.inchem.org/documents/jecfa/jecmono/v042je17.htm.

Madyastha, K.M. and Srivatsan, V., 1988
Biotransformations of alpha-terpineol in the rat: Its effects on the liver microsomal cytochrome P-450 system. Bull. envir. Contam. Toxicol., 41, 17-25.

Merck, 2013
The Merck Index. An Encyclopedia of Chemicals, Drugs and Biologicals. Ed. O'Neil MJ et al. Fifteenth edition. Royal Society of Chemistry, Cambridge, UK.

NCI
Short-term test program sponsored by the Division of Cancer Biology, National Cancer Institute. Ms Ellen Zaika, Assistant Project Officer, p. Y84.

NTP
US National Toxicology Program. Accessed September 2013. Available at: http://ntp.niehs.nih.gov/?objectid=03C9AF75-E1BF-FF40-DBA9EC0928DF8B15 and http://tools.niehs.nih.gov/ntp_tox/index.cfm

Oda, Y., Hamono, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1978
Mutagenicity of food flavours in bacteria (1st report). Osaka-Furitsu Koshu Eisei Kekyu Shokuhin Eisei Hen, 9, 177-181 (in Japanese, tables in English).

Santucci, B., Cristaudo, A., Cannistraci, C., Picardo, M., 1987
Contact dermatitis to fragrances. Contact Dermatitis, 16, 93-95.

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

Sigma-Aldrich
Accessed September 2013. Available at: http://www.sigmaaldrich.com/united-kingdom.html

Sigma-Aldrich, 2012
Material Safety Datasheet (MSDS) for Terpineol (8000-41-7), Revision 9 August 2012. Available at: http://www.sigmaaldrich.com/united-kingdom.html

SRC, 2013
Syracuse Research Corporation. Interactive PhysProp Database Demo. Incluing record for 2-(4-methyl-3-cylohexenyl)isopropanol (10482-56-1). 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.

Talapin, V.I., Palant, L.G., Krysanova, A.I., Chaikaoskaya, I.A., Bazylchik, V.V., 1987
Toxicological characteristics of terpenol, a new growth stimulant for agricultural plants. Gig. Truda prof. Zabol., 31, 29-31.

Toxtree
Estimation of toxic hazard – a decision tree approach. Ideaconsult Ltd. (Version 2.6.0). Accessed August 2013. Available for download at: http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/qsar_tools/toxtree