

Additive Toxicity Statement

Phenyl acetic acid



DESCRIPTION

Name Phenyl acetic acid

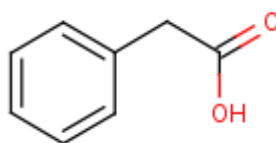
IUPAC name Phenylacetic acid

CAS no 103-82-2

EINECS no. 203-148-6

Molecular formula $C_8H_8O_2$

Structural formula



Molecular weight (g/mol.) 136.15

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.

Additive Toxicity Statement

Phenyl acetic acid



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

Additive Toxicity Statement

Phenyl acetic acid



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/scenih_r_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/scenih_r_o_051.pdf.

Additive Toxicity Statement

Phenyl acetic acid



REFERENCES

Alfa Aesar

Accessed March 2013. Available at: <http://www.alfa.com/en/go160w.pgm?srchtyp=product>

Anderson, H.H., Shimkin, M.B., Leake, C.D., 1936

Acute intraperitoneal toxicity of some plant growth substances for mice. *Proc. Soc. exp. Biol. Med.*, 34, 138-139.

BASF, 2002

Report from BASF to TSCA. Available at: [http://yosemite.epa.gov/oppts/epatscat8.nsf/by+Service/4A4EAC7BB189FFCF85256FAC005A5179/\\$File/89030000086.pdf](http://yosemite.epa.gov/oppts/epatscat8.nsf/by+Service/4A4EAC7BB189FFCF85256FAC005A5179/$File/89030000086.pdf)

Boggs, D.E., Rosenberg, R., Waisman, H.A., 1963

Effects of phenylalanine, phenylacetic acid, tyrosine, and valine on brain and liver serotonin in rats. *Proc. Soc. exp. Biol. Med.*, 114, 356-358.

Burdock, G.A., 2010

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

ChemIDplus

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

ChemSpider

Royal Society of Chemistry chemical structure database. Accessed March 2013. Available at: <http://www.chemspider.com/>

CoE, 2000

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

Culley, W.J., Saunders, R.N., Mertz, E.T., Jolly, D.H., 1962

Effect of phenylalanine and its metabolites on the brain serotonin level of the rat. *Proc. Soc. exp. Biol. Med.*, 111, 444-446.

Denno, K.M. and Sadler, T.W., 1990

Phenylalanine and its metabolites induce embryopathies in mouse embryos in culture. *Teratology*, 42, 565-570.

ECHA

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

EFSA

European Food Safety Authority. Accessed December 2014. Available at: <http://www.efsa.europa.eu/>

EFSA, 2009

Additive Toxicity Statement

Phenyl acetic acid



European Food Safety Authority. Flavouring Group Evaluation 53, Revision 1 (FGE.53Rev1): Consideration of phenethyl alcohol, aldehyde, acid and related acetals and esters evaluated by JECFA (59th meeting) and structurally related to phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in FGE.14Rev1 (2009) and one phenoxyethyl ester evaluated in FGE.23Rev1 (2008). Scientific Opinion of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids. *EFSA J.*, 1024, 1-42. Available at: <http://www.efsa.europa.eu/en/efsajournal/doc/1024.pdf>

EFSA, 2008

European Food Safety Authority. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) on a request from the Commission. Flavouring Group Evaluation 53 (FGE.53)

Consideration of phenethyl alcohol, aldehyde, acid and related acetals and esters evaluated by JECFA (59th meeting) structurally related to phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in FGE.14 (2005) and one phenoxyethyl ester evaluated in FGE.23 (2006). Available at: <http://www.efsa.europa.eu/en/efsajournal/doc/710.pdf>

Elf Atochem, 1997

Report dated 19th December 1997 submitted to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e). Available at: [http://yosemite.epa.gov/oppts/epatscat8.nsf/by+Service/6C51850BADE15D4485256F9B00509C74/\\$File/88980000066.pdf](http://yosemite.epa.gov/oppts/epatscat8.nsf/by+Service/6C51850BADE15D4485256F9B00509C74/$File/88980000066.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

EPISuite

Accessed March 2013. The database is available to download at: <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm>

FDA, 2011

Food and Drug Administration. Everything added to Food in the United States (EAFUS). Last updated 17 November 2011. Accessed March 2013. Available at: <http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=eafusListing>

Fisher Scientific, 2011

Material safety datasheet: phenylacetic acid, last revised 15 December 2011. Available at: https://extranet.fisher.co.uk/chemicalProductData_uk/wercs?itemCode=13028-5000

Flavis

EUROPA food flavouring website. Accessed March 2013. Available at: http://ec.europa.eu/food/food/chemicalsafety/flavouring/database/dsp_search.cfm

GESTIS

GESTIS Substance Database (Information system on hazardous substances of the German Social Accident Insurance). Accessed March 2013. Available at: [http://gestis-en.itrust.de/nxt/gateway.dll/gestis_en/000000.xml?f=templates\\$fn=default.htm\\$3.0](http://gestis-en.itrust.de/nxt/gateway.dll/gestis_en/000000.xml?f=templates$fn=default.htm$3.0)

Additive Toxicity Statement

Phenyl acetic acid



Good Scents Company

Accessed March 2013. Available at: <http://www.thegoodscentscompany.com/>

HSDB, 2008

Hazardous Substances Data Bank. Last revision date 22 April 2008. 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/>

IUCLID, 2000

International Uniform Chemical Information Database. Record for phenyl acetic acid. Available at: http://esis.jrc.ec.europa.eu/doc/IUCLID/data_sheets/103822.pdf

JECFA

Joint Expert Committee on Food Additives. Monographs and Evaluations. Accessed December 2014. Available at: <http://www.inchem.org/pages/jecfa.html>

JECFA, 2002

Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series: 50. Phenylethyl alcohol, aldehyde, acid and related acetals and esters and related substances. Available at:

<http://www.inchem.org/documents/jecfa/jecmono/v50je11.htm>

Katz, A.E., 1946

Dermal irritating properties of essential oils and aromatic chemicals. *Spice Mill*, 69, 46-51.

Lake, B.G., Longland, R.C., Harris, R.A., Collins, M.A., Herod, I.A., Gangolli, S.D., 1980

The effect of treatment with some phase II substrates on hepatic xenobiotic metabolism and the urinary excretion of metabolites of the d-glucuronic acid pathway in the rat. *Toxic. appl. Pharmac.*, 52, 371-378.

Loo, Y.H., Fulton, T., Miller, K., Wisniewski, H.M., 1980

Phenylacetate and brain dysfunction in experimental phenylketonuria: synaptic development. *Life Sci.*, 27(14), 1283-1290.

Loo, Y.H., Potempska, A., Wisniewski, H.M., 1985

A biochemical explanation of phenyl acetate neurotoxicity in experimental phenylketonuria. *J. Neurochem.*, 45, 1596-1600.

Maganova, N.B. and Zaitsev, A.N., 1973

A study into embryotoxic effect of some synthetic foodstuff aromatizers [author's translation]. *Vop. Pitan.*, Issue no. 4, 50-54. [Also cited in Chem. Abstr. 80: 44565u.]

Merck, 2006

The Merck Index. An Encyclopedia of Chemicals, Drugs and Biologicals. Ed. O'Neil J et al, Fourteenth edition. Merck & Co., Ltd., Whitehouse Station, NJ, USA.

Additive Toxicity Statement

Phenyl acetic acid



NRC, 1977

National Research Council. Drinking water and health. Volume 1. National Academy Press. p754-5. http://books.nap.edu/openbook.php?record_id=1780&page=R1

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/>

Opdyke, D.L.J., 1975

Monographs on fragrance raw materials: Phenylacetic acid. *Fd Cosmet. Toxicol.*, 12, 901-902.

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

Sherwin, C.P. and Kennard, K.S., 1919

Toxicity of phenylacetic acid. *J. biol. Chem.*, 40, 259-264.

Sigma-Aldrich

Accessed March 2013. Available at: <http://www.sigmaaldrich.com/united-kingdom.html>

SRC, 2013

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

Stewart, G.A., 1962

Pharmacological studies on oral hypoglycaemic agents. *Anglo-Germ. med. Rev.*, 1 334-347.

Toxtree

Estimation of toxic hazard – a decision tree approach. Ideaconsult Ltd. (Version 2.5.1). Accessed March 2013. Available for download at: http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/qsar_tools/toxtree

Vollmuth, T.A., Bennett, M.B., Hoverman, A.M., Christian, M.S., 1990

An evaluation of food flavoring ingredients using an *in vivo* reproductive and developmental toxicity screening test. *Teratology*, 41, 597.

Wen, G.Y., Wisniewski, H.M., Shek, J.W., Loo, Y.H., Fulton, T.R., 1980

Neuropathology of phenylacetate poisoning in rats: an experimental model of phenylketonuria. *Ann. Neurol.*, 7, 557-566.

Zaitsev, A.N. and Maganova, N.B., 1975

Embryotoxic action of some food aromatizers [author's translation]. *Vop. Pitan.*, Issue no. 3, 64-68.

Zaitsev, A.N. and Rakhmania, N.L., 1974

Additive Toxicity Statement

Phenyl acetic acid



Toxic properties of phenylethanol and cinnamic alcohol derivatives. *Vop. Pitan.*, Issue no. 5, 48-53.