

Additive Toxicity Statement

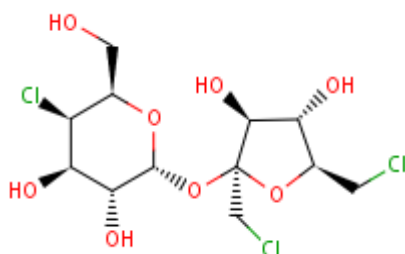
Sucralose



DESCRIPTION

Name	Sucralose
IUPAC name	(2R,3R,4R,5R,6R)-2-[(2R,3S,4S,5S)-2,5-bis(chloromethyl)-3,4-dihydroxyoxolan-2-yl]oxy-5-chloro-6-(hydroxymethyl)oxane-3,4-diol.
CAS no	56038-13-2
EINECS no.	259-952-2
Molecular formula	C ₁₂ H ₁₉ Cl ₃ O ₈

Structural formula



Molecular weight (g/mol)	397.633
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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
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

Alfa Aesar

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

Bigal, M.E. and Krymchantowski, A.V., 2006

Migraine triggered by sucralose – a case report. *Headache*, 46, 515-517.

Brusick, D., Grotz, V.L., Slesinski, R., Kruger, C.L., Hayes, A.W., 2010

The absence of genotoxicity of sucralose. *Fd Chem. Toxic.*, 48, 3067-3072.

Burdock, G.A., 2010

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

ChemIDplus

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

ChemSpider

Royal Society of Chemistry chemical structure database. Record for sucralose (56038-13-2). Accessed June 2013. Available at: <http://www.chemspider.com/>

CoE, 2000

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

CoE, 1981

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

COT, 2000

UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Annual report 2000. Available at: http://archive.food.gov.uk/pdf_files/cotcomcocrep_cot.pdf

Durnev, A.D., Oreshchenko, A.V., Kulakova, A.V., Beresten, N.F., Seredenin, S.B., 1995

Clastogenic activity of dietary sugar substitutes. *Vop. med. Khim.*, 41, 31-33 [in Russian; cited from abstract].

ECHA

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

EFSA

European Food Safety Authority. Accessed June 2013. Available at: <http://www.efsa.europa.eu/>

EPA

US Environmental Protection Agency. Integrated Risk Information System (IRIS). Accessed June 2013. http://www.epa.gov/iris/search_keyword.htm

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EPISuite

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

Finn, J.P. and Lord, G.H., 2000

Neurotoxicity studies on sucralose and its hydrolysis products with special reference to histopathologic and ultrastructural changes. *Fd Chem. Toxic.*, 38S2, S7-S17.

Fisher Scientific

Accessed June 2013. Available at: <http://www.fisher.co.uk/index.php/en/technical-support>

Flavis

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

GESTIS

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

Goldsmith, L.A., 2000

Acute and subchronic toxicity of sucralose. *Fd Chem. Toxic.*, 38, S53-S69.

Good Scents Company

Record for sucralose (56038-13-2). Accessed June 2013. Available at:
<http://www.thegoodscentscompany.com/>

HSDB

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

IARC

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

JECFA

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

JECFA, 1989

Joint FAO/WHO Expert Committee on Food Additives. Toxicological evaluation of certain food additives and contaminants. WHO Food Additive Series, 24, thirty-third meeting, Trichlorogalactosucrose. Available at:
<http://www.inchem.org/documents/jecfa/jecmono/v024je05.htm>

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JECFA, 1991

Joint FAO/WHO Expert Committee on Food Additives. Toxicological evaluation of certain food additives and contaminants. WHO Food Additive Series, 28, thirty-seventh meeting, Trichlorogalactosucrose. Available at: <http://www.inchem.org/documents/jecfa/jecmono/v28je14.htm>

Jeffrey, A.M. and Williams, G.M., 2000

Lack of DNA-damaging activity of five non-nutritive sweeteners in the rat hepatocyte/DNA repair assay. *Fd Chem. Toxic.*, 38, 335-338.

JRC

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

Kille, J.W., Tesh, J.M., McAnulty, P.A., Ross, F.W., Willoughby, C.R., Bailey, G.P., Wilby, O.K., Tesh, S.A., 2000a

Sucralose: assessment of teratogenic potential in the rat and rabbit. *Fd Chem. Toxic.*, 38 (Suppl. 2), S43-S52.

Kille, J.W., Ford, W.C., McAnulty, P., Tesh, J.M., Ross, F.W., Willoughby, C.R., 2000b

Sucralose: lack of effects on sperm glycolysis and reproduction in the rat. *Fd Chem. Toxic.*, 38 (Suppl. 2), S19-S29.

Mann, S.W., Yuschak, M.M., Amyes, S.J., Aughton, P., Finn, J.P., 2000a

A combined chronic toxicity/carcinogenicity study of sucralose in Sprague-Dawley rats. *Fd Chem. Toxic.*, 38 (Suppl. 2), S71-S89.

Mann, S.W., Yuschak, M.M., Amyes, S.J., Aughton, P., Finn, J.P., 2000b

A carcinogenicity study of sucralose in the CD-1 mouse. *Fd Chem. Toxic.*, 38 (Suppl. 2), S91-S98.

McLean Baird, I., Shephard, N.W., Merritt, R.J., Hildick-Smith, G., 2000

Repeated dose study of sucralose tolerance in human subjects. *Fd Chem. Toxic.*, 38, S123-S129.

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.

NICNAS, 2001

Australian National Industrial Chemicals Notification and Assessment Scheme. Full Public Report on 1,6-dichloro-1,6-dideoxy- β -D-fructofuranosyl-4-chloro-4-deoxy- α -D-galactose. File No. NA/944, November 2001. Available at: <http://www.nicnas.gov.au/publications/car/new/na/nafullr/na0900fr/na944fr.pdf>

NTP

US National Toxicology Program. Accessed June 2013. Available at http://tools.niehs.nih.gov/ntp_tox/index.cfm

Patel, R.M., Sarma, R., Grimsley, E., 2006

Popular sweetener [sic] sucralose as a migraine trigger. Headache, 46, 1303-1304.

Rocha, G.S., Pereira, M.O., Benarroz, M.O., Frydman, J.N., Rocha, V.C., Pereira, M.J., Fonseca, A.S., Medeiros, A.C., Bernardo-Filho, M., 2011

Sucralose sweetener in vivo effects on blood constituents radiolabeling, red blood cell morphology and radiopharmaceutical biodistribution in rats. Appl. Radiat. Isotopes, 69, 46-51.

Sasaki, Y.F., Kawaguchi, S., Kamaya, A., Ohshita, M., Kabasawa, K., Iwama, K., Taniguchi, K., Tsuda, S., 2002

The comet assay with 8 mouse organs: results with 39 currently used food additives. Mutation Res., 519, 103-119.

SCENIHR, 2010

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

SCF, 2000

Opinion of the Scientific Committee on Food on sucralose. SCF/CS/ADD/EDUL/190 Final adopted on 7 September 2000. Available at: http://ec.europa.eu/food/fs/sc/scf/out68_en.pdf

Sigma-Aldrich

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

SRC, 2013

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

Toxtree

Estimation of toxic hazard – a decision tree approach. Ideaconsult Ltd. (Version 2.5.4). Accessed June 2013. Available for download at: http://ihcp.jrc.ec.europa.eu/our_labs/computational_toxicology/qsar_tools/toxtree

Vanschewijck, P.M., Teredesai, A., Terpstra, P.M., Verbeeck, J., Kuhl, P., Gerstenberg, B., Gebel, S., Carmines, E.L., 2002

Evaluation of the potential effects of ingredients added to cigarettes. Part 4: Subchronic inhalation toxicity. Food and Chemical Toxicology, 40, 113-131.

Viberg, H. and Fredriksson, A., 2011

Neonatal exposure to sucralose does not alter biochemical markers of neuronal development or adult behavior. Nutrition, 27, 81-85.

World Health Organization, 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.