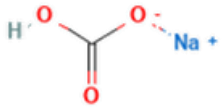
Additive Toxicity Statement

Sodium Bicarbonate

DESCRIPTION

Name	Sodium Bicarbonate
IUPAC name	Sodium;hydrogen carbonate
CAS no	144-55-8
EINECS no.	205-633-8
Molecular formula	$NaHCO_3$
Structural formula	
Molecular weight (g/mol)	84.01

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. 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

3V Sigma S.p.A *et al*. (2023). REACH registration dossier on sodium hydrogencarbonate (CAS RN 144-55-8) disseminated on the European Chemicals Agency (ECHA) website. First published 02-Mar-2011. Last modified 09-Mar-2023. https://echa.europa.eu/registration-dossier/-/registered-dossier/16157/1/2

Al-Abri SA and Olson KR (2013). Baking soda can settle the stomach but upset the heart: Case files of the Medical Toxicology fellowship at the university of California, San Francisco. Journal of Medical Toxicology 9, 255-258 (cited in Diaconu *et al.,* 2022).

Albrizio M, Lacalandra GM and Cinone M (2022). The role of bicarbonate in the modulation of capacitation, spontaneous acrosome reaction and motility of equine fresh and frozen spermatozoa. Theriogenology 187, 112-118 (from abstract only).

Alépée N, Grandidier MH and Cotovio J (2019). Usefulness of the EpiSkin™ reconstructed human epidermis model within Integrated Approaches on Testing and Assessment (IATA) for skin corrosion and irritation. Toxicology in Vitro 54, 147-167.

Baur X (2013). A compendium of causative agents of occupational asthma. Journal of Occupational Medicine and Toxicology 8, 15.

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

ChemSpider. Royal Society of Chemistry chemical structure database. Record for sodium bicarbonate (CAS RN 144-55-8). Accessed Oct-2023. http://www.chemspider.com/Chemical-Structure.8609.html

Csekő K, Hargitai D, Draskóczi L, Kéri A, Jaikumpun P, Kerémi B, Helyes Z and Zsembery Á (2022). Safety of chronic hypertonic bicarbonate inhalation in a cigarette smoke-induced airway irritation guinea pig model. BMC Pulmonary Medicine 22, 131.

Diaconu A, Florea I, Vlad CE, Achiței R and Florea L (2022). Metabolic alkalosis-an adverse effect of baking soda misuse: A case report and literature review. Experimental and Therapeutic Medicine 24, 658.

EC (2008a). European Commission. List of flavourings and source materials as laid down in Part I of Annex I of Regulation (EC) No 1334/2008. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:354:0034:0050:en:PDF

EC (2008b). European Commission. Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex:32008R1334

ECHA (a). European Chemicals Agency. Candidate list of substances of very high concern (SVHC) for authorisation. Accessed Oct-2023. https://echa.europa.eu/candidate-list-table

ECHA (b). European Chemicals Agency. Authorisation list. Accessed Oct-2023. https://echa.europa.eu/authorisation-list

ECHA (2023). European Chemicals Agency. Substance infocard for sodium hydrogencarbonate (CAS RN 144-55-8). Last updated 14-Mar-2023. https://echa.europa.eu/substance-information/-/substanceinfo/100.005.122

ED Lists (2023). Endocrine Disruptor Lists. Last updated Feb-2023. https://edlists.org/the-ed-lists

EFSA. European Food Safety Authority. Accessed Oct-2023. https://www.efsa.europa.eu/en

EFSA (2018). European Food Safety Authority. Peer review of the pesticide risk assessment of the active substance sodium hydrogen carbonate. EFSA Journal 16(9), 540. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5407

EMA. European Medicines Agency. Medicines Database. Accessed Mmm-YYYY. https://www.ema.europa.eu/en/medicines

EPA (a). US Environmental Protection Agency. Integrated Risk Information System (IRIS). Accessed Oct-2023. https://iris.epa.gov/AtoZ/?list_type=alpha

EPA (b). US Environmental Protection Agency. CompTox chemicals dashboard. Physchem Prop. Record for sodium bicarbonate (CAS RN 144-55-8). Accessed Oct-2023. https://comptox.epa.gov/dashboard/chemical/properties/DTXSID9021269

EPA (2012). US Environmental Protection Agency. Preliminary human health assessment for the registration review of potassium bicarbonate and sodium bicarbonate. 1 June 2012.

EU (2018). European Union. Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. Current consolidated version 01-Jan-2018. Document 02011R1169-20180101, Annex II. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02011R1169-20180101

Eyuboglu M (2016). Ventricular tachycardia or not? An unexpected reason of wide QRS complex tachycardia in a young healthy man: Sodium bicarbonate. Cardiovascular Toxicology 16, 406-408 (cited in HSDB, 2018).

FDA (2023a). US Food & Drug Administration. Substances added to food inventory. Last updated24-Aug-2023. https://www.accessdata.fda.gov/scripts/fdcc/?set=FoodSubstances

FDA (2023b). US Food & Drug Administration. Title 21 - Food and drugs. Chapter I - Food and Drug Administration. Department of Health and Human Services. Subchapter D - Drugs for Human Use. Part 331 - Antacid products for over-the-counter (OTC) human use. Subpart B - Active Ingredients. Sec. 331.11 Listing of specific active ingredients. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=331.11

FEMA Flavor Ingredient Library. Flavor and Extract Manufacturers Association of the United States. Accessed Oct-2023. https://www.femaflavor.org/flavor-library

Fitzgibbons LJ and Snoey ER (1999). Severe metabolic alkalosis due to baking soda ingestion: Case reports of two patients with unsuspected antacid overdose. The Journal of Emergency Medicine 17, 57-61 (cited in Diaconu *et al.,* 2022).

GESTIS (2023). Institute for Occupational Safety and Health of the German Social Accident Insurance Database. Last updated Apr-2023. https://limitvalue.ifa.dguv.de/

Go SM, Lee B, Ahn C, Jeong SH, Jo NR, Park SM, Lee M, Tran DN, Jung EM, Lee SD and Jeung EB (2023). Initial phase establishment of an *in vitro* method for developmental neurotoxicity test using Ki-67 in human neural progenitor cells. Journal of Physiology and Pharmacology 74 (from abstract only).

Good Scents Company. Record for sodium bicarbonate (CAS Number 144-55-8). Accessed Nov-2023. www.thegoodscentscompany.com/data/rw1099761.html

Gróf I, Bocsik A, Harazin A, Santa-Maria AR, Vizsnyiczai G, Barna L, Kiss L, Fűr G, Rakonczay Z Jr, Ambrus R, Szabó-Révész P, Gosselet F, Jaikumpun P, Szabó H, Zsembery Á and Deli MA (2020). The effect of sodium bicarbonate, a beneficial adjuvant molecule in cystic fibrosis, on bronchial epithelial cells expressing a wild-type or mutant CFTR channel. International Journal of Molecular Sciences 21, 4024 (from abstract only).

Grotegut CA, Dandolu V, Katari S, Whiteman V, Geifman-Holtzman O and Teitelman M (2006). A case of hypokalemic metabolic alkalosis and rhabdomyolysis in pregnancy. Obstetrics & Gynecology 107, 484-486 (cited in HSDB, 2018).

Hilton NP, Leach NK, Sparks SA, Gough LA, Craig MM, Deb SK and McNaughton LR (2019). A novel ingestion strategy for sodium bicarbonate supplementation in a delayed-release form: A randomised crossover study in trained males. Sports Medicine - Open 5, 4.

HSDB (2018). Hazardous Substances Data Bank. Record for sodium bicarbonate (CAS RN 144-55-8). Last revision date 18-Dec-2018. https://pubchem.ncbi.nlm.nih.gov/source/hsdb/697

IARC (2023). International Agency for Research on Cancer. List of classifications, Volumes 1–134.Last updated 11-Oct-2023. https://monographs.iarc.who.int/list-of-classifications

JECFA. Joint FAO/WHO Expert Committee on Food Additives. Portal. Accessed Oct-2023. https://apps.who.int/food-additives-contaminants-jecfa-database/

JECFA (1967). Joint FAO/WHO Expert Committee on Food Additives. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids and bases. F.A.O. Nutrition Meeting Report Series 40A,B,C. Ninth and Tenth Reports of the Joint FAO/WHO Expert Committee on Food Additives. https://iris.who.int/bitstream/handle/10665/39853/WHO_TRS_339.pdf?sequence=1

Johnson W and Swanson K (1987). Final report on the safety assessment of sodium sesquicarbonate, sodium bicarbonate, and sodium carbonate. Journal of the American College of Toxicology 6, 121-138 (cited in OECD, 2007).

Jones RL, Stellingwerff T, Artioli GG, Saunders B, Cooper S and Sale C (2016). Dose-response of sodium bicarbonate ingestion highlights individuality in time course of blood analyte responses. International Journal of Sport Nutrition and Exercise Metabolism 26, 445-453 (from abstract only).

Lazebnik N, Iellin A and Michowitz M (1986). Spontaneous rupture of the normal stomach after sodium bicarbonate ingestion. Journal of Clinical Gastroenterology 8, 454-456 (cited in Diaconu *et al.,* 2022).

Lhasa (2022). Carcinogenicity database. Record for sodium bicarbonate (CAS RN 144-55-8). https://carcdb.lhasalimited.org/study-information/44483544

Mennen M and Slovis CM (1988). Severe metabolic alkalosis in the emergency department. Annals of Emergency Medicine 17, 354-357 (cited in Diaconu *et al.,* 2022).

NTP (2021). National Toxicology Program. Fifteenth report on carcinogens (RoC). Released 21-Dec-2021. https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html

OECD (2002). Organisation for Economic Co-operation and Development. SIDS Initial Assessment Report for SIAM 15. Sodium bicarbonate. https://hpvchemicals.oecd.org/UI/handler.axd?id=e1859b4e-f6a4-4da8-8945-6294354cdf45

OECD (2007). Organisation for Economic Co-operation and Development. SIDS Initial Assessment Report For SIAM 22. Bicarbonate special. https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?id=60A61B06-671D-4D58-9E96-B822E49BE0DD

OEHHA (2023). California Office of Environmental Health Hazard Assessment) Proposition 65 list. Dated 11-Aug-2023. https://oehha.ca.gov/proposition-65/proposition-65-list

Okada H, Inoue T, Takahira S, Sugahara S, Nakamoto H and Suzuki H (1999). Daytime hypertension, sleep apnea and metabolic alkalosis in a haemodialysis patient-the result of sodium bicarbonate abuse. Nephrology, Dialysis, Transplantation 14, 452-454 (cited in Diaconu *et al.,* 2022).

PubChem (2023). An open chemistry database at the National Institutes of Health (NIH). Record for sodium bicarbonate (CAS RN 144-55-8). Created 27-Mar-2005. Last modified 21-Oct-2023. https://pubchem.ncbi.nlm.nih.gov/compound/516892

Rowe RC, Sheskey PJ and Quinn ME (2009). Handbook of Pharmaceutical Excipients. 6th Edition Published by: Pharmaceutical Press and American Pharmacists Association, ISBN 978 0 85369 792 3 (UK).

Sarwal A, Kim S, Gnanasekaran I (2021). Life-threatening alkalosis from baking soda pica in an end stage renal disease hemodialysis patient. Hemodialysis International 26, E16-E18 (from abstract only).

Scolari Childress KM and Myles T (2013). Baking soda pica associated with rhabdomyolysis and cardiomyopathy in pregnancy. Obstetrics and Gynecology 122, 495-497 (cited in Diaconu *et al.,* 2022).

Siegler JC, Carr AJ, Jardine WT, Convit L, Cross R, Chapman D, Burke LM and Ross M (2022). The hyperhydration potential of sodium bicarbonate and sodium citrate. International Journal of Sport Nutrition and Exercise Metabolism 32, 74-81 (from abstract only).

Solak Y, Turkmen K, Atalay H and Turk S (2009). Baking soda induced severe metabolic alkalosis in a haemodialysis patient. NDT Plus 2, 280-281 (cited in Diaconu *et al.,* 2022).

Sparks A, Williams E, Robinson A, Miller P, Bentley DJ, Bridge C and McNaughton LR (2017). Sodium bicarbonate ingestion and individual variability in time-to-peak pH. Research in Sports Medicine 25, 58-66 (from abstract only).

Toxtree. Estimation of toxic hazard - a decision tree approach. Ideaconsult Ltd. (Version 3.1.0). Accessed Oct-2023. Available for download at: http://toxtree.sourceforge.net/

Vásquez A, Domínguez C and Perdomo CF (2017). Spontaneous gastric rupture after Sodium Bicarbonate consumption: A case report. Radiography (London) 23, e62-e64.

WAO (2019). World Allergy Organization. Quirce S and Sastre J, Sensitizing agents inducers of occupational asthma, hypersensitivity pneumonitis and eosinophilic bronchitis. Updated Jul-2019. http://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/occupational-allergens/

Wnorowski G (1992). EPA Dermal Irritation Test. Product Safety Labs, New Jersey, USA (cited in OECD, 2002, 2007).

Wong DW, Mishkin FS and Tanaka TT (1980). Journal of the American Medical Association 244, 61-62 (cited in HSDB, 2018).

APPENDIX

Statement:
This ingredient has been assessed by BAT for its toxicity and carcinogenic, mutagenic or toxic for reproduction (CMR) properties. Based on an investigation of available and relevant internal and external data, it has been concluded that this ingredient does not have any CMR properties. Furthermore, this ingredient is not subject to a harmonised classification as CMR under CLP (1272/2008).