Food Safety AUTHORITY OF IRELAND

TOXICOLOGY FACTSHEET SERIES

ISSUE NO. 3 | NOVEMBER 2015

Aspartame

This factsheet is intended for food business operators, enforcement officers and other interested parties. It:

- Provides background information on the sweetener aspartame
- Includes the relevant legislation governing the use of aspartame
- Provides information on the labelling requirements for phenylketonuria sufferers and
- Outlines the safety assessments that aspartame has undergone since it was first approved for use in the European Union

1. Background

Aspartame (E951) has been used as a sweetener in foods and as a table-top sweetener for more than 30 years in many countries throughout the world. Aspartame is the methyl ester of the dipeptide of two amino acids, phenylalanine and aspartic acid. It is an odourless, white crystalline powder which has a clean, sweet taste. It is referred to as an intense (or artificial) sweetener and is used to replace sugar in a wide range of sugar-free and low-calorie foods such as drinks, desserts, sweets, dairy products, chewing gums, energy-reduced and weight control products, as well as its use as a table-top sweetener. It has the same calorific value as sugar, but is about 200 times sweeter than sugar and so only a small amount is needed to sweeten products. Aspartame is sometimes referred to under its original trade name of 'Nutrasweet'.

2. Legislation on Sweeteners[1]

Sweeteners such as aspartame are classified as food additives, and their use in food is controlled in the European Union by Regulation 1333/2008/EC as amended (EU, 2008). The legislation stipulates that only authorised additives may be used in the manufacture or preparation of foodstuffs. A new additive which requires authorisation in the EU must go through a safety assessment by the European Food Safety Authority (EFSA). Prior to the establishment of EFSA in 2002, this function was carried out by the EU Scientific Committee on Food (SCF).

The manufacturer of any potential new additive must not only produce evidence that there is a real need for the substance, but must also commission research into the safety of the substance. The research must include a battery of toxicological tests (to determine whether a substance is harmful). These include tests to assess the neurotoxicity, reproductive effects, genotoxic and carcinogenic potential of the compound. Following favourable evaluation of a particular additive, it is placed on the EU 'positive list' of approved additives as set out in Annex II Part B of Regulation 1333/2008/EC.

The maximum levels at which additives such as aspartame may be used and also the specific foodstuffs in which they may be used and their conditions of use are laid down in Regulation 1333/2008/EC. These levels are set at values which ensure that a person consuming a typical diet would not exceed the Acceptable Daily Intake (ADI[2]) established for the additive in question. In the case of sweeteners such as aspartame, the levels are set

[1] https://www.fsai.ie/legislation/food_legislation/food_additives/food_additives_legislation.html

[2] ADI-If an additive is deemed acceptable for food use, an Acceptable Daily Intake is normally set. The concept of the ADI was established by the Joint Expert Committee on Food Additives (JECFA) and is defined as: "an estimate of the amount of food additive, expressed on a body weight basis that can be ingested daily over a lifetime without appreciable health risk."

Aspartame

at values which will protect particularly vulnerable populations such as diabetics, who must avoid sugar-containing food and drinks, and children who are known to consume larger quantities of beverages such as fizzy drinks and squashes that may be sweetened using aspartame. Currently, the maximum permitted levels (MPLs) for aspartame range from 25 to 6,000 mg/kg in foods, except for table-top sweeteners where aspartame is authorised *quantum satis*[3].

In Ireland, the use of sweeteners in foodstuffs is controlled by European Union (Food Additives) Regulations, 2015, S.I. No. 330 of 2015. These Regulations give effect to Regulation (EC) No 1333/2008 and to Commission Regulation (EU) No 231/2012 (EU 2012) which lays down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008. Dietary intake of food additives in Ireland has been evaluated and it has been shown that the general population does not exceed the ADIs for sweeteners, including aspartame.

3. Labelling Warning for Phenylketonuria Sufferers

A small group of people cannot safely consume aspartame. These are individuals with the inherited disease phenylketonuria (PKU), who are unable to metabolise the amino acid phenylalanine effectively, resulting in high levels of phenylalanine and low levels of tyrosine in the blood. High blood phenylalanine levels are toxic to the brain and can, if left untreated, affect brain development and cause intellectual disability, mood disorders and behavioural problems. PKU is a serious metabolic disorder which is normally diagnosed shortly after birth by a routine blood test. Most treatment of PKU aims to keep blood phenylalanine at acceptable levels by restriction of foods rich in protein (meat, fish, eggs, dairy products, nuts and seeds), many starchy foods, including those containing flour (bread, pasta), as well as foods and drinks containing aspartame which is an additional source of phenylalanine.

Under EU and Irish legislation, all food products containing aspartame or aspartame-acesulfame salt, designated in the list of ingredients by their specific name, should be clearly labelled with the words "contains a source of phenylalanine", on the label. If aspartame (E 951) or aspartame-acesulfame salt (E 962) is designated in the list of ingredients only by reference to the E-number, then the label must state "contains aspartame (a source of phenylalanine)". This labelling requirement is intended to alert those who suffer from PKU to avoid consuming these products.

4. Reviews of the Safety of Aspartame

Aspartame was evaluated by the SCF in 1984, 1988 and 2002 (SCF 1985, 1989, 2002), and more recently in 2006, 2009, 2011 and 2013 by EFSA (EFSA 2006, 2009a, 2009b, 2011, 2013). In their evaluations of 2006, 2009 and 2011, EFSA considered new carcinogenicity studies on aspartame carried out by the European Ramazzini Foundation (ERF), Bologna, Italy (Soffritti *et al.*, 2005, 2006, 2007 and 2010). The EFSA opinion of 2011 also looked at the association between intakes of artificially sweetened soft drinks and pre-term delivery in pregnant women (Halldorsson *et al.*, 2010). In 2013, EFSA issued an opinion on the re-evaluation of aspartame taking into account all available scientific research on the additive and its breakdown products, e.g. phenylalanine, methanol and aspartic acid, including both animal and human studies. This latest EFSA opinion on aspartame is outlined in more detail below.

Aspartame has only been authorised for use and included in the EU 'positive list' of approved additives after a rigorous safety assessment. All approvals of food additives are kept under review by the regulatory authorities as and when scientific and medical information becomes available on possible adverse effects, not previously recognised or reported.

[3] *Quantum satis* shall mean that no maximum numerical level is specified and substances shall be used in accordance with good manufacturing practice, at a level not higher than is necessary to achieve the intended purpose and provided the consumer is not misled.

Aspartame

In 2011, the European Commission asked EFSA to bring forward their re-evaluation of the safety of aspartame, which was due to be completed by 2020 under Regulation 257/2010/EU (EU, 2010), to 2013 after concerns about the safety of aspartame were raised by members of the European Parliament. This was due to reports which indicated a possible link with epilepsy and brain tumours, headaches, allergies, and behavioural changes and/or changes in cognitive function. Concerns have also been raised about the possibility of toxicity from methanol, one of the breakdown products of aspartame.

This EFSA re-evaluation of aspartame in 2013 was one of the most comprehensive risk assessments ever undertaken on the sweetener (EFSA, 2013). This rigorous review of aspartame considered all available information and following a detailed analysis of both animal and human studies based on the most up-to-date scientific knowledge, claims linking consumption of aspartame to development of serious disorders such as multiple sclerosis, lupus erythematosis, Gulf War Syndrome, chronic fatigue syndrome, and diabetes mellitus were considered to be anecdotal, with no reliable scientific evidence to substantiate that aspartame might be responsible for these conditions.

EFSA concluded that aspartame is not genotoxic or carcinogenic, having extensively re-reviewed the results and all data from the animal carcinogenicity studies on aspartame from the European Ramazzini Foundation (ERF), Bologna, Italy, a scientific institute involved in research into cancer (Soffritti *et al.*, 2005, 2006, 2007, 2010). The authors of the ERF studies considered on the basis of their results, that aspartame had carcinogenic potential, since rodents fed aspartame for a lifetime developed cancers at various sites, including tumours of the blood cells, kidney, peripheral nerves, liver and lungs. EFSA concluded that there were other underlying explanations for the occurrence of the tumours seen in these studies other than exposure to aspartame and that these studies did not cause EFSA concerns about possible health effects for consumers of aspartame (EFSA, 2006 & 2011). EFSA concluded, on the basis of the information available from these ERF studies, that there was no reason to further review the safety of aspartame, or to revise the current ADI of 40 mg/kg body weight established by the SCF. EFSA also stated that consumer intake of aspartame in a number of European countries (up to 10 mg/kg body weight) is well below this figure, even in high consumers.

EFSA's experts also concluded that aspartame does not harm the brain, the nervous system or affect behaviour or cognitive function in children or adults. With respect to pregnancy, EFSA noted that there was no risk to the developing foetus from exposure to phenylalanine derived from aspartame at the current ADI (with the exception of women suffering from PKU). Danish researchers reported findings suggesting that the daily intake of artificially sweetened soft drinks may be associated with an increased risk of pre-term delivery (Halldorsson, 2010). EFSA also examined this Danish study in its 2013 review of aspartame and concluded that there was no evidence available to support a causal relationship between the consumption of artificially sweetened soft drinks and pre-term delivery.

The opinion on aspartame also states that the breakdown products of aspartame (phenylalanine, methanol and aspartic acid) are also naturally present in other foods (for instance, methanol is found in fruit and vegetables). The contribution of breakdown products of aspartame to the overall dietary exposure to these substances is low. In relation to the formation of methanol, the amounts derived from aspartame, which are approximately 10% by weight, are less than those found naturally in other foods and are not considered to pose a risk. Methanol may be present in or can be released from foods including fruits, fruit juices, vegetables, roasted coffee, honey and alcoholic beverages. In fruit juices, concentrations vary widely (1-640 mg methanol/L) with an average of 140 mg/L (WHO, 1997). By far the largest amount of methanol in humans (some 90% on average) is produced naturally by the body from the consumption of pectin-containing fruits such as apples and citrus fruits (EFSA, 2013).

Aspartame

Overall, EFSA concluded once again that new data did not give reason to reconsider the previous evaluations of aspartame or of the other food additive sweeteners authorised in the European Union. Current exposure to aspartame is below the ADI. Overall, EFSA (2013) concluded that the ADI of 40mg/kg bw/day established by the SCF (1984, 1988 and 2002), did not need to be revised and is protective for the general population. However, in patients suffering from the medical condition phenylketonuria (PKU), the ADI is not applicable as they require strict adherence to a diet low in phenylalanine.

Aspartame has also been previously evaluated by other regulatory bodies such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1975, 1976, 1980, 1981), the United States Food and Drug Administration (FDA, 1984), the UK Committee on Toxicity (COT, 1992) and the Agence Française de Sécurité Sanitaire des Aliments[4] (AFSSA, 2002). The FDA has reviewed all complaints alleging adverse reactions to products containing aspartame since 1985 but has failed to determine any consistent pattern of symptoms that can be attributed to the use of aspartame. The FDA has also stated that analysis of the National Cancer Institute database on cancer incidence in the USA does not support an association between the use of aspartame and increased incidence of brain tumours (FDA, 1996), a conclusion restated by the SCF (SCF, 2002). The French Agency AFSSA also concluded in 2002 that aspartame was not genotoxic and that the previously conducted carcinogenicity tests in rodents did not indicate a relationship between treatment with aspartame and the appearance of brain tumours (AFSSA, 2002). Both JECFA and the SCF established an ADI of 40 mg/kg body weight (bw)/day, which was subsequently endorsed by EFSA.

5. Surveillance of Additives in Foods available on the Irish Market

The Food Safety Authority of Ireland (FSAI), among its activities, coordinates the collation of food safety surveillance information from laboratories run by its official agencies. Aspartame is tested in a variety of foodstuffs on an annual basis as part of the National Chemical Surveillance programme agreed between the FSAI and the Health Service Executive (HSE). Over two hundred and thirty samples of food have been tested in 2013 and 2014 for aspartame and of these, two were non-compliant with the legislation as they contained aspartame that was not declared on the label. The FSAI also conducts targeted food safety surveillance in areas where potential safety issues have been identified. In 2005 and 2006, the FSAI carried out a targeted surveillance study on levels of artificial sweeteners including aspartame in foods available on the Irish market. The results of this survey showed that, of over 300 samples analysed, all were found to contain levels of aspartame below the maximum level permitted by the legislation, and four products contained aspartame that was not declared on the label (FSAI, 2007).

Exposure to aspartame from its use as a food additive has been calculated using the EFSA European Consumption Database (Comprehensive Database[5]), which includes Irish adult food consumption data. The consumption data are coupled with maximum permitted levels as laid down in Regulation 1333/2008/EC and also with data on reported use levels or data on measured levels in foods which were submitted to EFSA by either industry or Member States including Ireland (EFSA, 2013). Exposure to the sweetener was also calculated for Irish pre-school children (1-4 years) using the National Pre-School Nutrition Survey (NPNS) in conjunction with the maximum permitted levels as laid down in Regulation 1333/2008/EC (Martyn, Connolly, McNulty, Nugent & Gibney, 2014). Results of these exposure assessments are given in Table 1.

[4] AFSSA changed its name to ANSES-French Agency for Food, Environmental and Occupational Health and Safety on the 1 July 2010.

[5] http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm

Aspartame

Table 1. Summary of total estimated exposure to aspartame (as a food additive) for the Irish adult[6] and pre-school children population: mean and high level[7] (mg/kg bw/day)

POPULATION	MEAN INTAKE LEVEL	HIGH INTAKE LEVEL
Adults (NSIFCS)[8]	3.1	8.2
Pre-school children (NPNS)[9]	4.2	16.4

The results of these exposure assessments show that the exposure of the Irish adult and pre-school children populations to aspartame as a food additive is well below the ADI of 40 mg/kg bw/day. Using chemical concentration data from the National Food Chemical Sampling programme, instead of the maximum permitted levels laid down in the additives Regulation and used in the exposure calculations in Table 1 above, allowed a more refined exposure assessment to be carried out for the pre-school children. This resulted in a mean and high intake levels for aspartame of 0.66 and 2.72 mg/kg bw/day respectively, which is considerably lower than the most conservative estimate of exposure as outlined in Table 1 for this population group.

6. Conclusion

The safety of aspartame has been extensively studied over the years and experts worldwide agree that aspartame is safe for use. This has been restated by the EU Scientific Committee for Food in 2002 and by EFSA in 2006, 2009, 2011 and most recently, in 2013. On all of these occasions, EFSA concluded that the new scientific data did not give reason to review the safety evaluation of aspartame or to revise the ADI. In terms of types of studies and the amounts given to human subjects in controlled studies, aspartame is one of the most thoroughly tested food additives.

7. References

AFSSA (Agence française de sécurité sanitaire des aliments), 2002. AFSSA report on the question of a possible link between exposure to aspartame and brain tumours. Maisons-Alfort, request number 2000-SA-0249. Report in French, available at http://www.afssa.fr

Commission Regulation (EU) No 1333/2008 of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p.16)

Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council OJ L 83, 22.3.2012 p 1-295

Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a program for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p.19-27

COT (UK Committee on toxicity of chemicals in food, consumer products and the environment), (1992). Annual report of the Committees on Toxicity, Mutagenicity, Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. The Stationary Office, London

[6] Estimated exposure for the Irish population was the same when usage data which was supplied by industry was used in the calculation (EFSA, 2013).

[7] 95th percentile

[8] North/South Ireland Food Consumption Survey (NSIFCS) (18-64 year olds)

[9] The National Pre-School Nutrition Survey (NPNS) (1-4 years)

Aspartame

EFSA (European Food Safety Authority), 2006. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) related to a new long-term carcinogenicity study on aspartame. *EFSA Journal* 2006, 356, 1-44
http://www.efsa.europa.eu/en/efsajournal/pub/356.htm

EFSA (European Food Safety Authority), 2009a. Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on a request from the European Commission related to the 2nd ERF carcinogenicity study on aspartame. *EFSA Journal* 2009, 945, 1-18

EFSA (European Food Safety Authority), 2009b. Updated Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on a request from the European Commission related Opinion on the re-evaluation of aspartame (E951) as a food additive. *EFSA Journal* 2013;11(12):3496 166 to the 2nd ERF carcinogenicity study on aspartame taking into consideration study data submitted by the Ramazzini Foundation in February 2009. *EFSA Journal* 2009, 1015, 1-18
http://www.efsa.europa.eu/en/efsajournal/pub/1015.htm

EFSA (European Food Safety Authority), 2013. Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on a request from the European Commission for the re-evaluation of aspartame (E 951) as a food additive. *EFSA Journal* 2013;11 (12):3496
http://www.efsa.europa.eu/en/efsajournal/doc/3496.pdf

EFSA (European Food Safety Authority), 2011. EFSA Statement on the scientific evaluation of two studies related to the safety of artificial sweeteners. *EFSA Journal* 2011;9 (2):2089, 16 pp. doi:10.2903/j.efsa.2011.2089 http://www.efsa.europa.eu/en/efsajournal/pub/2089.htm

European Union (Food Additives) Regulations, 2015 (S.I. No. 330 of 2015)
http://health.gov.ie/wp-content/uploads/2015/07/si330.pdf

FDA (United States Food and Drug Administration),1984. Food additives permitted for direct addition to food for human consumption: aspartame. *Federal Register* 49: 6672-6677

FDA (United States Food and Drug Administration),1996. Food and Drug Administration Statement on Aspartame. Talk Paper T96-74, November 18, 1996

FSAI (Food Safety Authority of Ireland), 2007. Surveillance study on levels of artificial colours and sweeteners in Irish retail products
https://www.fsai.ie/uploadedFiles/Monitoring_and_Enforcement/Monitoring/Surveillance/Colours%20and%20sweeteners%20survey.pdf

Halldorsson T.I. *et al.*, Intake of artificially sweetened soft drinks and risk of pre-term delivery: a prospective cohort study in 59,334 Danish pregnant women. *Am. J. Clin. Nutr.* 2010, 92, 626-33

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1975. Evaluation of certain food additives: some food colours, thickening agents, smoke condensates, and certain other substances. WHO Food Additives Series No. 6 World Health Organization, Geneva

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1976. Evaluation of certain food additives. Twentieth Report. World Health Organization, Geneva

Aspartame

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1980. Toxicological evaluation of certain food additives: aspartame. WHO Food Additives Series No 15, World Health Organization, Geneva

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1981. Toxicological evaluation of certain food additives: aspartame. WHO Food Additives Series No. 16, World Health Organization, Geneva

Martyn, D., Connolly, A., McNulty, B., Nugent, A., & Gibney, M. (2014). Report to the FSAI on the estimation of intake of four intense sweeteners by Irish pre-school children (1-4 years) (unpublished)

SCF (EU Scientific Committee on Food),1985. Sweeteners. Reports of the Scientific Committee for Food (Sixteenth Series), EUR 10210 EN, Commission of the European Communities, Luxembourg. Report available at: http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_16.pdf

SCF (EU Scientific Committee on Food) 1989. Sweeteners. Reports of the Scientific Committee for Food (Twenty-first Series), EUR 11617 EN, Commission of the European Communities, Luxembourg

SCF (EU Scientific Committee on Food), 2002. Opinion of the Scientific Committee on Food: Update on the Safety of Aspartame (expressed on 4 December 2002). Available at http://ec.europa.eu/food/fs/sc/scf/out155_en.pdf

Soffritti M, Belpoggi F, Esposti DD and Lambertini L, 2005. Aspartame induces lymphomas and leukaemias in rats. *European Journal of Oncology*, 10,107–116

Soffritti M, Belpoggi F, Degli Esposti D, Lambertini L, Tibaldi E and Rigano A, 2006. First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. *Environmental Health Perspectives*, 114, 379-385

Soffritti M, Belpoggi F, Tibaldi E, Degli Esposti D and Lauriola M, 2007. Life-span exposure to low doses of aspartame beginning during pre-natal life increases cancer effects in rats. *Environmental Health Perspectives*, 115, 1293-1297

Soffritti M, Belpoggi F, Manservigi M, Tibaldi E, Lauriola M, Falcioni L and Bua L, 2010. Aspartame administered in feed, beginning pre-natally through life span, induces cancers of the liver and lung in male Swiss mice. *American Journal of Industrial Medicine*, 53, 1197-1206

WHO (World Health Organization), 1997. Methanol. *Environmental Health Criteria* 196. Available online: http://www.inchem.org/documents/ehc/ehc/ehc196.htm