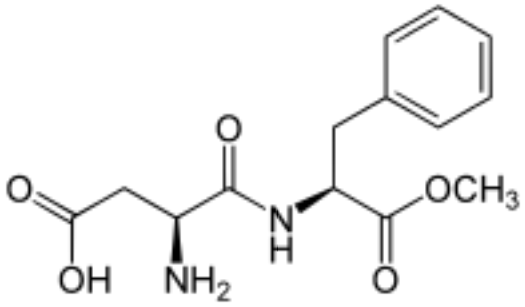
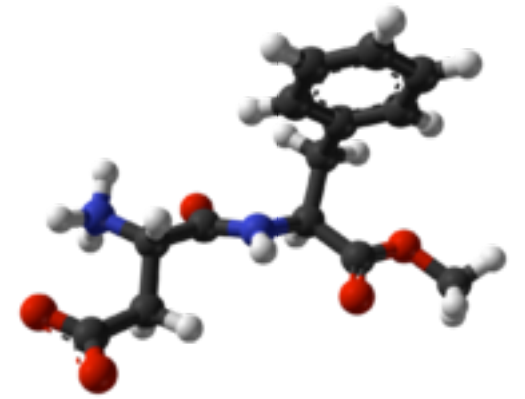
Aspartame

From Wikipedia, the free encyclopedia

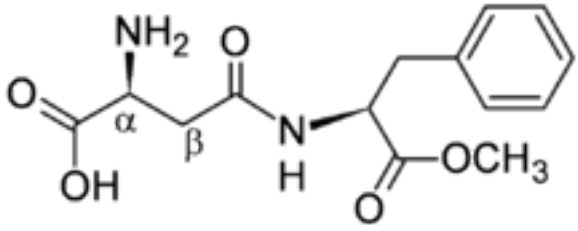




Names		
Pronunciation	/ˈæspərteɪm/ or /əˈspɑːrteɪm/	
IUPAC name Methyl L-α-aspartyl-L-phenylalaninate		
Other names *N*-(L-α-Aspartyl)-L-phenylalanine, 1-methyl ester		
Identifiers		
CAS Number	1	22839-47-0✓
3D model (JSmol)	1	Interactive image

ChEBI	1 CHEBI:2877✓
ChemSpider	1 118630✓
DrugBank	1 DB00168✓
ECHA InfoCard	100.041.132
EC Number	245-261-3
E number	E951 (glazing agents, ...)
KEGG	1 C11045✓
PubChem CID	1 134601
UNII	1 Z0H242BBR1✓
InChI [show]	
SMILES [show]	
Properties	
Chemical formula	$C_{14}H_{18}N_2O_5$
Molar mass	294.31 g·mol^{-1}
Density	1.347 g/cm^3
Melting point	246 to 247 °C (475 to 477 °F; 519 to 520 K)
Boiling point	decomposes
Solubility in water	Sparingly soluble
Solubility	Slightly soluble in ethanol
Acidity (pK_a)	4.5–6.0[2]
Hazards[3]	
GHS pictograms	
GHS signal word	Danger
GHS hazard statements	H312, H332
GHS precautionary statements	P260, P261, P264, P270, P271, P280, P302+352, P304+312, P304+340, P312, P314, P322, P363, P501
NFPA 704	 1 1 0

Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa).
✓ verify (what is ✓✗ ?)
Infobox references



Beta-aspartame differs from aspartame based upon which carboxyl group of aspartate binds to the nitrogen of phenylalanine.

Aspartame (**APM**) is an artificial, non-saccharide sweetener used as a sugar substitute in some foods and beverages. In the European Union, it is codified as E951. Aspartame is a methyl ester of the aspartic acid/phenylalanine dipeptide.

A panel of experts set up by the European Food Safety Authority concluded in 2013 that aspartame is safe for human consumption at current levels of exposure,[4] As of 2017 evidence does not support a long-term benefit for weight loss or in diabetes.[5][6] Because its breakdown products include phenylalanine, people with the genetic condition phenylketonuria (PKU) must be aware of this as an additional source.[7]

It was first sold under the brand name NutraSweet. It was first made in 1965, and the patent expired in 1992. It was initially approved for use in food products by the U.S. Food and Drug Administration (FDA) in 1981.[8]:2 The safety of aspartame has been the subject of several political and medical controversies, United States congressional hearings, and Internet hoaxes.[9][10][11]

Uses[edit]

Aspartame is approximately 200 times sweeter than sucrose (table sugar). Due to this property, even though aspartame produces four kilocalories of energy per gram (17 kJ/g) when metabolized, the quantity of aspartame needed to produce a sweet taste is so small that its caloric contribution is negligible.[12] The taste of aspartame and other artificial sweeteners differs from that of table sugar in the times of onset and how long the sweetness lasts, though aspartame comes closest to sugar's taste profile among approved artificial sweeteners.[13] The sweetness of aspartame lasts longer than that of sucrose, so it is often blended with other artificial sweeteners such as acesulfame potassium to produce an overall taste more like that of sugar.[14]

Like many other peptides, aspartame may hydrolyze (break down) into its constituent amino acids under conditions of elevated temperature or high pH. This

makes aspartame undesirable as a baking sweetener, and prone to degradation in products hosting a high pH, as required for a long shelf life. The stability of aspartame under heating can be improved to some extent by encasing it in fats or in maltodextrin. The stability when dissolved in water depends markedly on pH. At room temperature, it is most stable at pH 4.3, where its half-life is nearly 300 days. At pH 7, however, its half-life is only a few days. Most soft-drinks have a pH between 3 and 5, where aspartame is reasonably stable. In products that may require a longer shelf life, such as syrups for fountain beverages, aspartame is sometimes blended with a more stable sweetener, such as saccharin.[15]

Descriptive analyses of solutions containing aspartame report a sweet aftertaste as well as bitter and off-flavor aftertastes.[16] In products such as powdered beverages, the amine in aspartame can undergo a Maillard reaction with the aldehyde groups present in certain aroma compounds. The ensuing loss of both flavor and sweetness can be prevented by protecting the aldehyde as an acetal.

Health effects[edit]

The safety of aspartame has been studied since its discovery.[17] Aspartame is one of the most rigorously tested food ingredients.[18] As of 2017 evidence does not support a benefit for weight loss or in diabetes with some data finding an association with weight gain and heart disease risks.[5][6]

Reviews by governmental regulatory bodies have found aspartame safe for consumption at current levels.[12][17][19][20] Aspartame has been deemed safe for human consumption by over 100 regulatory agencies in their respective countries,[20] including the UK Food Standards Agency,[21] the European Food Safety Authority (EFSA)[22] and Health Canada.[23]

Weight[edit]

Two 2017 systematic review and meta-analysis found that aspartame consumption had no significant effect on variables related to obesity and diabetes.[6][5] Nonnutritive sweeteners are also linked with increased weight and heart disease risk.[5]

Phenylketonuria[edit]

High levels of the naturally occurring essential amino acid phenylalanine are a health hazard to those born with phenylketonuria (PKU), a rare inherited disease that prevents phenylalanine from being properly metabolized. Since individuals with PKU must consider aspartame as an additional source of phenylalanine, foods containing aspartame sold in the United States must state "Phenylketonurics: Contains Phenylalanine" on their product labels.[24]

In the UK, foods that contain aspartame are legally required by the country's Food Standards Agency to list the substance among the product's ingredients and carry the warning "Contains a source of phenylalanine" – this is usually at the foot of the list of

ingredients. Manufacturers are also required to print "'with sweetener(s)" on the label close to the main product name on foods that contain "sweeteners such as aspartame" or "with sugar and sweetener(s)" on "foods that contain both sugar and sweetener".[25]

In Canada, foods that contain aspartame are legally required by the country to list the substance among the product's ingredients and include a measure of the amount of aspartame per serving. As well, labels must state that the product contains phenylalanine – this is usually in the order of ingredients, contained in brackets.[26]

Phenylalanine is one of the essential amino acids and is required for normal growth and maintenance of life. Concerns about the safety of phenylalanine from aspartame for those without phenylketonuria center largely on hypothetical changes in neurotransmitter levels as well as ratios of neurotransmitters to each other in the blood and brain that could lead to neurological symptoms. Reviews of the literature have found no consistent findings to support such concerns,[20] and while high doses of aspartame consumption may have some biochemical effects, these effects are not seen in toxicity studies to suggest aspartame can adversely affect neuronal function.[12] Like methanol, common foods in the typical diet, such as milk, meat, and fruits, will lead to ingestion of significantly higher amounts of phenylalanine than would be expected from aspartame consumption.[20]

Breast feeding[edit]

In a study done in 1979, the effect of aspartame ingestion on blood and milk amino acid levels in lactating women was tested.[27] In this study, six women from the ages of 20 to 29 with established lactation were studied after oral administration of aspartame or lactose (50 mg/kg body weight) in a random order, with the intent to study the differences in breast milk between the two. The study resulted with the conclusion that aspartame administration at 50 mg/kg body weight has a small effect upon the milk aspartate levels; and, although a small increase in aspartate time-effect scores was noted over the four-hour postabsorptive period, no significant difference was noted over the entire 24-hour watching period.[27]

Cancer[edit]

Reviews have found no association between aspartame and cancer. These reviews have looked at numerous carcinogenicity studies in animals, epidemiologic studies in humans, as well as *in vitro* genotoxicity studies. These studies have found no significant evidence that aspartame causes cancer in animals, damages the genome, or causes cancer in humans at doses currently used.[12][17][20][28][29] This position is supported by multiple regulatory agencies like the FDA[30] and EFSA as well as scientific bodies such as the National Cancer Institute.[31] Aspartame did not show any DNA-damaging properties either.[32]

Concern about possible carcinogenic properties of aspartame was originally raised and popularized in the mainstream media by John Olney in the 1970s and again in 1996 by suggesting that aspartame may be related to brain tumors. Reviews have

found that these concerns were flawed, due to reliance on the ecological fallacy[32] and the purported mechanism of causing tumors being unlikely to actually cause cancer. Independent agencies such as the FDA and National Cancer Institute have reanalyzed multiple studies based on these worries and found no association between aspartame and brain cancer.[20]

As discussed in the article on controversies around aspartame, the Cesare Maltoni Cancer Research Center of the European Ramazzini Foundation of Oncology and Environmental Sciences released several studies which claimed that aspartame can increase several malignancies in rodents, concluding that aspartame is a potential carcinogen at normal dietary doses.[33][34] The EFSA[35] and the FDA[30] discounted the study results due to lack of transparency and numerous flaws in the study, finding no reason to revise their previously established acceptable daily intake levels for aspartame.

Neurological and psychiatric symptoms[edit]

Numerous allegations have been made via the Internet and in consumer magazines purporting neurotoxic effects of aspartame leading to neurological or psychiatric symptoms such as seizures, headaches, and mood changes.[12] Review of the biochemistry of aspartame has found no evidence that the doses consumed would plausibly lead to neurotoxic effects.[36] Comprehensive reviews have not found any evidence for aspartame as a cause for these symptoms.[12][17][20] One review did provide a theoretical biochemical background of neurotoxicity and suggested further testing.[37] However, a panel of EFSA experts noted that this review's conclusions were partially based on Internet sources and therefore were not scientifically robust. These experts also concurred with a critique that significant scientific errors were made in the critical review that led to unsubstantiated and misleading interpretations.[17] A review of studies on children did not show any significant findings for safety concerns with regard to neuropsychiatric conditions such as panic attacks, mood changes, hallucinations or with ADHD or seizures.[38]

Headaches[edit]

Headaches are the most common symptom reported by consumers.[12] While one small review noted aspartame is likely one of many dietary triggers of migraines, in a list that includes "cheese, chocolate, citrus fruits, hot dogs, monosodium glutamate, aspartame, fatty foods, ice cream, caffeine withdrawal, and alcoholic drinks, especially red wine and beer,"[39] other reviews have noted conflicting studies about headaches[12][40] and still more reviews lack any evidence and references to support this claim.[17][20][38]

Safety[edit]

Main article: Aspartame controversy

Aspartame has been found to be safe for human consumption by more than ninety countries worldwide,[41][42] with FDA officials describing aspartame as "one of the most thoroughly tested and studied food additives the agency has ever approved" and its safety as "clear cut",[43] but has been the subject of several controversies, hoaxes[9] and health scares.[44]

Initially, aspartame was approved by the U.S. Food and Drug Administration (FDA) in 1974; however, problems with Searle's safety testing program, including testing of aspartame, were discovered subsequently. The approval was rescinded the following year; but, after outside reviews of the problematic tests and additional testing, final approval was granted in 1981. Because allegations of conflicts of interest marred the FDA's approval of aspartame,[8][43][45] the U.S. Government Accountability Office reviewed the actions of involved officials in 1986 and the approval process in 1987; neither the allegations of conflict of interest nor problems in the final approval process were substantiated.[8][46]

In addition, the Centers for Disease Control investigated in 1984 and was unable to find any significant epidemiological associations to serious risk or harm.[47]

Since December 1998, a widely circulated email hoax has cited aspartame as the cause of numerous diseases.[48]

The weight of existing scientific evidence indicates that aspartame is safe at current levels of consumption as a non-nutritive sweetener.[12] Reviews conducted by regulatory agencies decades after aspartame was first approved have supported its continued availability.[49]

Mechanism of action[edit]

The perceived sweetness of aspartame (and other sweet substances like acesulfame K) in humans is due to its binding of the heterodimer G-protein coupled receptor formed by the proteins TAS1R2 and TAS1R3.[50]

Metabolites[edit]

Aspartame is rapidly hydrolyzed in the small intestines. Even with ingestion of very high doses of aspartame (over 200 mg/kg), no aspartame is found in the blood due to the rapid breakdown.[12] Upon ingestion, aspartame breaks down into residual components, including aspartic acid, phenylalanine, methanol,[51] in ratio of 4:5:1 by mass[52] and further breakdown products including formaldehyde[53] and formic acid. Human studies show that formic acid is excreted faster than it is formed after ingestion of aspartame. In some fruit juices, *higher* concentrations of methanol can be found than the amount produced from aspartame in beverages.[54]

Aspartame's major decomposition products are its cyclic dipeptide (in a 2,5-diketopiperazine, or DKP, form), the de-esterified dipeptide (aspartyl-phenylalanine), and its constituent components, phenylalanine,[55] aspartic acid,[54] and methanol.[56] At 180 °C, aspartame undergoes decomposition to form a diketopiperazine derivative.[57]

Aspartate[edit]

Aspartic acid (aspartate) is one of the most common amino acids in the typical diet. As with methanol and phenylalanine, intake of aspartic acid from aspartame is less than would be expected from other dietary sources. At the 90th percentile of intake, aspartame provides only between 1% and 2% of the daily intake of aspartic acid. There has been some speculation[58][59] that aspartame, in conjunction with other amino acids like glutamate, may lead to excitotoxicity, inflicting damage on brain and nerve cells. However, clinical studies have shown no signs of neurotoxic effects,[12] and studies of metabolism suggest it is not possible to ingest enough aspartic acid and glutamate through food and drink to levels that would be expected to be toxic.[20]

Methanol[edit]

The methanol produced by the metabolism of aspartame is absorbed and quickly converted into formaldehyde and then completely oxidized to formic acid. The methanol from aspartame is unlikely to be a safety concern for several reasons. Fruit juices and citrus fruits contain methanol, and there are other dietary sources for methanol such as fermented beverages and the amount of methanol produced from aspartame-sweetened foods and beverages is likely to be less than that from these and other sources that are already in people's diets.[12] With regard to formaldehyde, it is rapidly converted in the body, and the amounts of formaldehyde from the metabolism of aspartame are trivial when compared to the amounts produced routinely by the human body and from other foods and drugs. At the highest expected human doses of consumption of aspartame, there are no increased blood levels of methanol or formic acid,[12] and ingesting aspartame at the 90th percentile of intake would produce 25 times less methanol than what would be considered toxic.[20]

Chemistry[edit]

Aspartame is a methyl ester of the dipeptide of the natural amino acids L-aspartic acid and L-phenylalanine. Under strongly acidic or alkaline conditions, aspartame may generate methanol by hydrolysis. Under more severe conditions, the peptide bonds are also hydrolyzed, resulting in free amino acids.[60]

While known aspects of synthesis are covered by patents, many details are proprietary.[13] Two approaches to synthesis are used commercially. In the chemical synthesis, the two carboxyl groups of aspartic acid are joined into an anhydride, and the amino group is protected by converting it to a functional group[*clarification needed*] that will not interfere in the next reaction. Phenylalanine is converted to its methyl ester and

combined with the *N*-protected aspartic anhydride; then the protecting group is removed from aspartic nitrogen by acid hydrolysis. The drawback of this technique is that a byproduct, the bitter-tasting β-form, is produced when the wrong carboxyl group from aspartic acid links to phenylalanine. A process using an enzyme from *Bacillus thermoproteolyticus* to catalyze the condensation of the chemically altered amino acids will produce high yields without the β-form byproduct. A variant of this method, which has not been used commercially, uses unmodified aspartic acid, but produces low yields. Methods for directly producing aspartyl-phenylalanine by enzymatic means, followed by chemical methylation, have also been tried, but not scaled for industrial production.[61]

Intake[edit]

The acceptable daily intake (ADI) value for aspartame, as well as other food additives studied, is defined as the "amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk."[62] The Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Commission's Scientific Committee on Food has determined this value is 40 mg/kg of body weight for aspartame,[63] while FDA has set its ADI for aspartame at 50 mg/kg.[31]

The primary source for exposure to aspartame in the United States is diet soft drinks, though it can be consumed in other products, such as pharmaceutical preparations, fruit drinks, and chewing gum among others in smaller quantities.[12] A 12 US fluid ounce (355 ml) can of diet soda contains 180 milligrams (0.0063 oz) of aspartame, and for a 75 kg (165 lb) adult, it takes approximately 21 cans of diet soda daily to consume the 3,750 milligrams (0.132 oz) of aspartame that would surpass the FDA's 50 milligrams per kilogram of body weight ADI of aspartame from diet soda alone.[31]

Reviews have analyzed studies which have looked at the consumption of aspartame in countries worldwide, including the United States, countries in Europe, and Australia, among others. These reviews have found that even the high levels of intake of aspartame, studied across multiple countries and different methods of measuring aspartame consumption, are well below the ADI for safe consumption of aspartame.[12][17][20][63] Reviews have also found that populations that are believed to be especially high consumers of aspartame such as children and diabetics are below the ADI for safe consumption, even considering extreme worst-case scenario calculations of consumption.[12][17]

In a report released on 10 December 2013, the EFSA said that, after an extensive examination of evidence, it ruled out the "potential risk of aspartame causing damage to genes and inducing cancer," and deemed the amount found in diet sodas an amount safe to consume.[64]

History[edit]

Aspartame was discovered in 1965 by James M. Schlatter, a chemist working for G.D. Searle & Company. Schlatter had synthesized aspartame as an intermediate step in generating a tetrapeptide of the hormone gastrin, for use in assessing an anti-ulcer drug candidate.[65] He discovered its sweet taste when he licked his finger, which had become contaminated with aspartame, to lift up a piece of paper.[12][66][67] Torunn Atteraas Garin participated in the development of aspartame as an artificial sweetener.[68]

In 1975, prompted by issues regarding Flagyl and Aldactone, a U.S. FDA task force team reviewed 25 studies submitted by the manufacturer, including 11 on aspartame. The team reported "serious deficiencies in Searle's operations and practices".[8] The FDA sought to authenticate 15 of the submitted studies against the supporting data. In 1979, the Center for Food Safety and Applied Nutrition (CFSAN) concluded, since many problems with the aspartame studies were minor and did not affect the conclusions, the studies could be used to assess aspartame's safety.[8]

In 1980, the FDA convened a Public Board of Inquiry (PBOI) consisting of independent advisors charged with examining the purported relationship between aspartame and brain cancer. The PBOI concluded aspartame does not cause brain damage, but it recommended against approving aspartame at that time, citing unanswered questions about cancer in laboratory rats.[8]:94–96[69]

Citing data from a Japanese study that had not been available to the members of the PBOI,[70] and after seeking advice from an expert panel that found fault with statistical analyses underlying the PBOI's hesitation, yet argued against approval,[8]:53 FDA commissioner Hayes approved aspartame for use in dry goods.[8] In 1983, the FDA further approved aspartame for use in carbonated beverages, and for use in other beverages, baked goods, and confections in 1993.[*citation needed*] In 1996, the FDA removed all restrictions from aspartame, allowing it to be used in all foods.[*citation needed*]

Several European Union countries approved aspartame in the 1980s, with EU-wide approval in 1994. The European Commission Scientific Committee on Food reviewed subsequent safety studies and reaffirmed the approval in 2002. The European Food Safety Authority reported in 2006 that the previously established Acceptable daily intake was appropriate, after reviewing yet another set of studies.[35]

Compendial status[edit]

- British Pharmacopoeia[71]
- United States Pharmacopeia[72]

Commercial uses[edit]

Under the trade names Equal, NutraSweet, and Canderel, aspartame is an ingredient in approximately 6,000 consumer foods and beverages sold worldwide, including (but not limited to) diet sodas and other soft drinks, instant breakfasts, breath

mints, cereals, sugar-free chewing gum, cocoa mixes, frozen desserts, gelatin desserts, juices, laxatives, chewable vitamin supplements, milk drinks, pharmaceutical drugs and supplements, shake mixes, tabletop sweeteners, teas, instant coffees, topping mixes, wine coolers and yogurt. It is provided as a table condiment in some countries. Aspartame is less suitable for baking than other sweeteners, because it breaks down when heated and loses much of its sweetness.

NutraSweet Company[edit]

In 1985, Monsanto Company bought G.D. Searle, and the aspartame business became a separate Monsanto subsidiary, the NutraSweet Company. In March 2000, Monsanto sold it to J.W. Childs Equity Partners II L.P.[73] European use patents on aspartame expired starting in 1987,[74] and the U.S. patent expired in 1992. Since then, the company has competed for market share with other manufacturers, including Ajinomoto, Merisant and the Holland Sweetener Company.

Ajinomoto[edit]

Many aspects of industrial synthesis of aspartame were established by Ajinomoto.[13] In 2004, the market for aspartame, in which Ajinomoto, the world's largest aspartame manufacturer, had a 40 percent share, was 14,000 metric tons a year, and consumption of the product was rising by 2 percent a year.[75] Ajinomoto acquired its aspartame business in 2000 from Monsanto for $67M.[76]

In 2008, Ajinomoto sued British supermarket chain Asda, part of Wal-Mart, for a malicious falsehood action concerning its aspartame product when the substance was listed as excluded from the chain's product line, along with other "nasties".[77] In July 2009, a British court found in favour of Asda.[78] In June 2010, an appeals court reversed the decision, allowing Ajinomoto to pursue a case against Asda to protect aspartame's reputation.[79] Asda said that it would continue to use the term "no nasties" on its own-label products,[80] but the suit was settled in 2011 with Asda choosing to remove references to aspartame from its packaging.[81]

In November 2009, Ajinomoto announced a new brand name for its aspartame sweetener – AminoSweet.[82]

Holland Sweetener Company[edit]

A joint venture of DSM and Tosoh, the Holland Sweetener Company manufactured aspartame using the enzymatic process developed by Toyo Soda (Tosoh) and sold as the brand Sanecta.[83] Additionally, they developed a combination aspartame-acesulfame salt under the brand name Twinsweet.[84] They left the sweetener industry in late 2006, because "global aspartame markets are facing structural oversupply, which has caused worldwide strong price erosion over the last five years", making the business "persistently unprofitable".[85]

Competing products[edit]

Because sucralose, unlike aspartame, retains its sweetness after being heated, and has at least twice the shelf life of aspartame, it has become more popular as an ingredient.[86] This, along with differences in marketing and changing consumer preferences, caused aspartame to lose market share to sucralose.[87][88] In 2004, aspartame traded at about $30/kg and sucralose, which is roughly three times sweeter by weight, at around $300/kg.[89]

Ant-killer hoax[edit]

Aspartame has been falsely claimed to have been originally developed as ant poison. The source for this was a satirical article posted on "thespoof" website.[90][91] Further claims that the substance actually is poisonous to ants were inferred from that online article being quoted as fact by various anti-aspartame websites, and videos of numerous trials of this rumor have been shown on YouTube, or posted on social networks, some even claiming success in eradicating ants with Aspartame or with other sweeteners.[90]

See also[edit]

- Aspartame controversy
- NutraSweet
- Stevia
- Phenylalanine ammonia lyase

References[edit]

1 ^ Budavari, Susan, ed. (1989). "861. Aspartame". *The Merck Index* (11th ed.). Rahway, NJ: Merck & Co. p. 859. ISBN 978-0-911910-28-5.

2 ^ Rowe, Raymond C. (2009). "Aspartame". *Handbook of Pharmaceutical Excipients*. pp. 11–12. ISBN 1-58212-058-7.

3 ^ "aspartame". *pubchem.ncbi.nlm.nih.gov*.

4 ^ "Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive". *EFSA Journal*. **11** (12): 263. 10 December 2013. doi:10.2903/j.efsa.2013.3496 (inactive 2017-01-28).

5 ^ Jump up to:
a b c d Azad, Meghan B.; Abou-Setta, Ahmed M.; Chauhan, Bhupendrasinh F.; Rabbani, Rasheda; Lys, Justin; Copstein, Leslie; Mann, Amrinder; Jeyaraman, Maya M.; Reid, Ashleigh E.; Fiander, Michelle; MacKay, Dylan S.; McGavock, Jon; Wicklow, Brandy; Zarychanski, Ryan (16 July 2017). "Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies". *Canadian Medical Association Journal*. **189** (28): E929–E939. doi:10.1503/cmaj.161390.

6 ^ Jump up to:
a b c Santos, NC; Araujo, LM; De Luca Canto, G; Guerra, EN; Coelho, MS; Borin, MF (10 April 2017). "Metabolic effects of aspartame in adulthood: a systematic review and meta-analysis of randomized clinical trials.". *Critical Reviews in Food Science and Nutrition*: 0. PMID 28394643. doi:10.1080/10408398.2017.1304358.

7 ^ "Additional Information about High-Intensity Sweeteners Permitted for use in Food in the United States". *FDA*. U.S. Food and Drug Administration. 26 May 2015. Retrieved 28 June 2017.

8 ^ Jump up to:
a b c d e f g h "U.S. GAO – HRD-87-46 Food and Drug Administration: Food Additive Approval Process Followed for Aspartame, 18 June 1987". Retrieved 5 September 2008.

9 ^ Jump up to:
a b Mikkelson, David (8 June 2015). "FALSE: Aspartame — Sweet Poison". *Snopes*. Retrieved 3 May 2017.

10 ^ "ACSH Debunks Internet Health Hoax". *acsh.org*. Archived from the original on 9 May 2013. Retrieved 15 January 2016.

11 ^ "A Web of Deceit". *TIME.com*. 8 February 1999. Retrieved 15 January 2016.

12 ^ Jump up to:
a b c d e f g h i j k l m n o p q Magnuson BA; Burdock GA; Doull J; et al. (2007). "Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies". *Critical Reviews in Toxicology*. **37** (8): 629–727. PMID 17828671. doi:10.1080/10408440701516184.

13 ^ Jump up to:
a b c O'Donnell, Kay (2006). "6 Aspartame and Neotame". In Mitchell, Helen Lucy. *Sweeteners and sugar alternatives in food technology*. Blackwell. pp. 86–95. ISBN 1-4051-3434-8. Retrieved 26 July 2011.

14 ^ "New Products Weigh In". foodproductdesign.com. Retrieved 19 June 2010.

15 ^ "Fountain Beverages in the US" (PDF). The Coca-Cola Company. May 2007. Archived from the original (PDF) on 20 March 2009.

16 ^ Nahon, Denise F.; JP Roozen; Cees de Graaf (February 1998). "Sensory Evaluation of Mixtures of Maltitol or Aspartame, Sucrose and an Orange Aroma". *Chem. Senses*. **23** (1): 59–66. PMID 9530970. doi:10.1093/chemse/23.1.59.

17 ^ Jump up to:
a b c d e f g h EFSA National Experts (May 2010). "Report of the meetings on aspartame with national experts". EFSA. Retrieved 9 January 2011.

18 ^ Mitchell, Helen (2006). *Sweeteners and sugar alternatives in food technology*. Oxford, UK: Wiley-Blackwell. p. 94. ISBN 1-4051-3434-8.

19 ^ Food Standards Australia New Zealand: "Food Standards Australia New Zealand: Aspartame – what it is and why it's used in our food". Archived from the original on 16 December 2008. Retrieved 9 December 2008.

20 ^ Jump up to:
a b c d e f g h i j k Butchko, H; Stargel, WW; Comer, CP; Mayhew, DA; Benninger, C;

Blackburn, GL; De Sonneville, LM; Geha, RS; Hertelendy, Z (2002). "Aspartame: Review of Safety". *Regulatory Toxicology and Pharmacology*. **35** (2 Pt 2): S1–93. PMID 12180494. doi:10.1006/rtph.2002.1542.

21 **^** "Aspartame". UK FSA. 17 June 2008. Archived from the original on 7 October 2010. Retrieved 23 September 2010.

22 **^** "Aspartame". EFSA. Archived from the original on 10 March 2011. Retrieved 23 September 2010.

23 **^** "Aspartame". Health Canada. Archived from the original on 22 September 2010. Retrieved 23 September 2010.

24 **^** "CFR - Code of Federal Regulations Title 21". *fda.gov*. Retrieved 15 January 2016.

25 **^** "Aspartame". *UK Food Standards Agency*. 19 March 2015. Retrieved 28 June 2017.

26 **^** "NGREDIENT S PECIFICATIONS NutraSweet ® Custom Powder" (PDF). NutraSweet. Archived from the original (PDF) on 8 May 2013. Retrieved 25 January 2014.

27 ^ Jump up to:
[a] [b] Stegink, L. D.; Filer Jr, L. J.; Baker, G. L. (1979). "Plasma, erythrocyte and human milk levels of free amino acids in lactating women administered aspartame or lactose". *The Journal of Nutrition*. **109** (12): 2173–81. PMID 512705.

28 **^** Marinovich, M; Galli, CL; Bosetti, C; Gallus, S; La Vecchia, C (October 2013). "Aspartame, low-calorie sweeteners and disease: regulatory safety and epidemiological issues.". *Food and Chemical Toxicology*. **60**: 109–15. PMID 23891579. doi:10.1016/j.fct.2013.07.040.

29 **^** Kirkland, D; Gatehouse, D (October 2015). ""Aspartame: A review of genotoxicity data".". *Food and Chemical Toxicology*. **84**: 161–8. PMID 26321723. doi:10.1016/j.fct.2015.08.021.

30 ^ Jump up to:
[a] [b] "US FDA/CFSAN – FDA Statement on European Aspartame Study". Archived from the original on 30 July 2010. Retrieved 23 September 2010.

31 ^ Jump up to:
[a] [b] [c] "Aspartame and Cancer: Questions and Answers". National Cancer Institute. 12 September 2006. Archived from the original on 12 February 2009. Retrieved 29 August 2011.

32 ^ Jump up to:
[a] [b] Weihrauch, M. R.; Diehl, V (2004). "Artificial sweeteners – do they bear a carcinogenic risk?". *Annals of Oncology*. **15** (10): 1460–5. PMID 15367404. doi:10.1093/annonc/mdh256.

33 **^** Soffritti, M.; Belpoggi, F.; Esposti, D.D.; Lambertini, L.; Tibaldi, E.; Rigano, A. (2006). "First Experimental Demonstration of the Multipotential Carcinogenic Effects of Aspartame Administered in the Feed to Sprague-Dawley Rats". *Environ Health Perspect*. **114** (3): 379–385. PMC 1392232. PMID 16507461. doi:10.1289/ehp.8711.

34 **^** Soffritti, M.; Belpoggi, F.; Tibaldi, E.; Esposti, D.D.; Lauriola, M. (2007). "Life-span exposure to low doses of aspartame beginning during prenatal life increases cancer

effects in rats". *Environ Health Perspect*. **115** (9): 1293–1297. PMC 1964906. PMID 17805418. doi:10.1289/ehp.10271.

35 ^ Jump up to:
[a] [b] Panel on Food Additives and Nutrient Sources added to Food (2006). "Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to a new long-term carcinogenicity study on aspartame". *The EFSA Journal*. **356** (5): 1–44. doi:10.2903/j.efsa.2006.356.

36 **^** Lajtha, A (1994). "Aspartame consumption: lack of effects on neural function". *The Journal of Nutritional Biochemistry*. **5** (6): 266–83. doi:10.1016/0955-2863(94)90032-9.

37 **^** Humphries, P; Pretorius, E; Naudé, H (2007). "Direct and indirect cellular effects of aspartame on the brain". *European Journal of Clinical Nutrition*. **62** (4): 451–62. PMID 17684524. doi:10.1038/sj.ejcn.1602866.

38 ^ Jump up to:
[a] [b] ""Inactive" Ingredients in Pharmaceutical Products: Update (Subject Review)". *Pediatrics*. **99** (2): 268–78. 1997. PMID 9024461. doi:10.1542/peds.99.2.268.

39 **^** Millichap, J; Yee, MM (2003). "The diet factor in pediatric and adolescent migraine". *Pediatric Neurology*. **28** (1): 9–15. PMID 12657413. doi:10.1016/S0887-8994(02)00466-6.

40 **^** Sun-Edelstein, Christina; Mauskop, Alexander (2009). "Foods and Supplements in the Management of Migraine Headaches". *The Clinical Journal of Pain*. **25** (5): 446–52. PMID 19454881. doi:10.1097/AJP.0b013e31819a6f65.

41 **^** Health Canada: "Aspartame – Artificial Sweeteners".

42 **^** Food Standards Australia New Zealand: "Food Standards Australia New Zealand: Aspartame (Updated January 2013)". Retrieved 26 November 2014.

43 ^ Jump up to:
[a] [b] Henkel, John (November–December 1999). "Sugar Substitutes: Americans Opt for Sweetness and Lite". *FDA Consumer*. DIANE Publishing. **33** (6): 12–6. ISBN 978-1-4223-2690-9. PMID 10628311. Archived from the original on 30 December 2016. Retrieved 29 January 2009.

44 **^** Flaherty, Megan (12 April 1999). "Harvesting Kidneys and other Urban Legends". *NurseWeek*. Archived from the original on 7 October 1999. Retrieved 7 March 2013.

45 **^** Sugarman, Carole (3 July 1983). "Controversy Surrounds Sweetener". *Washington Post*. pp. D1–2. Retrieved 25 November 2008.

46 **^** GAO 1986. "Six Former HHS Employees' Involvement in Aspartame's Approval." United States General Accounting Office, GAO/HRD-86-109BR, July 1986.

47 **^** Centers for Disease Control (CDC) (2 November 1984). "Evaluation of Consumer Complaints Related to Aspartame Use". *Morbidity and Mortality Weekly Report*. Centers for Disease Control and Prevention. **33** (43): 605–7. PMID 6436658. Retrieved 8 May 2012.

48 **^** "Aspartame Warning". About.com. – the Nancy Markle chain email.

49 **^** Reviews by:
EFSA 2012
USFDA 2007 Archived 29 July 2015 at the Wayback Machine.

50 ^ Li XD, Staszewski L, Xu H, Durick K, Zoller M, Adler E (2002). "Human receptors for sweet and umami taste". *Proc. Natl. Acad. Sci. U.S.A.* **99** (7): 4692–6. Bibcode:2002PNAS...99.4692L. PMC 123709. PMID 11917125. doi:10.1073/pnas.072090199.

51 ^ Roberts HJ (2004). "Aspartame disease: a possible cause for concomitant Graves' disease and pulmonary hypertension". *Texas Heart Institute Journal*. **31** (1): 105; author reply 105–6. PMC 387446. PMID 15061638.

52 ^ Humphries, P; Pretorius, E; Naudé, H (2008). "Direct and indirect cellular effects of aspartame on the brain". *Eur J Clin Nutrition*. **62** (4): 451–462. PMID 17684524. doi:10.1038/sj.ejcn.1602866.

53 ^ Trocho C; Pardo R; Rafecas I; et al. (1998). "Formaldehyde derived from dietary aspartame binds to tissue components in vivo". *Life Sciences*. **63** (5): 337–49. PMID 9714421. doi:10.1016/S0024-3205(98)00282-3.

54 ^ Jump up to:
[a] [b] Stegink, Lewis D. (July 1987). "The aspartame story: a model for the clinical testing of a food additive". *American Journal of Clinical Nutrition*. **46** (1): 204–15. PMID 3300262.

55 ^ Prodolliet, J.; Bruelhart, M. (1993). "Determination of aspartame and its major decomposition products in foods". *J AOAC Int*. **76** (2): 275–82. PMID 8471853.

56 ^ Lin, SY.; Cheng, YD. (October 2000). "Simultaneous formation and detection of the reaction product of solid-state aspartame sweetener by FT-IR/DSC microscopic system". *Food Addit Contam*. **17** (10): 821–7. PMID 11103265. doi:10.1080/026520300420385.

57 ^ Rastogi, S.; Zakrzewski, M.; Suryanarayanan, R. (March 2001). "Investigation of solid-state reactions using variable temperature X-ray powder diffractrometry. I. Aspartame hemihydrate". *Pharm Res*. **18** (3): 267–73. PMID 11442263. doi:10.1023/A:1011086409967.

58 ^ Olney, J. W. (1984). "Excitotoxic food additives – relevance of animal studies to human safety". *Neurobehav Toxicol Teratol*. **6** (6): 455–62. PMID 6152304.

59 ^ Rycerz, Karol; Jaworska-Adamu, Jadwiga Elżbieta (2013). "Effects of aspartame metabolites on astrocytes and neurons". *Folia Neuropathologica*. **1**: 10–17. doi:10.5114/fn.2013.34191. Retrieved 27 July 2013.

60 ^ Ager, David J.; Pantaleone, David P.; Henderson, Scott A.; Katritzky, Alan R.; Prakash, Indra & Walters, D. Eric (1998). "Commercial, Synthetic Non-nutritive Sweeteners". *Angewandte Chemie International Edition*. **37** (13–24): 1802–1817. doi:10.1002/(SICI)1521-3773(19980803)37:13/14<1802::AID-ANIE1802>3.0.CO;2-9.

61 ^ Yagasaki, Makoto; Hashimoto, Shin-ichi (November 2008). "Synthesis and application of dipeptides; current status and perspectives". *Applied Microbiology and Biotechnology*. **81** (1): 13–22. PMID 18795289. doi:10.1007/s00253-008-1590-3.

62 ^ WHO (1987). "Principles for the safety assessment of food additives and contaminants in food". *Environmental health criteria 70*.

63 ^ Jump up to:
[a] [b] Renwick, Andrew (2006). "The intake of intense sweeteners – an update review". *Food Additives & Contaminants*. **23** (4): 327–38. doi:10.1080/02652030500442532.

64 ^ "Aspartame in Soda is Safe: European Review". Associated Press. Retrieved 16 December 2013.

65 ^ Mazur, Robert H. (1974). "Aspartic acid-based sweeteners". In Inglett, George E. *Symposium: sweeteners*. Westport, CT: AVI Publishing. pp. 159–163. ISBN 0-87055-153-1. LCCN 73-94092.

66 ^ Lewis, Ricki (2001). *Discovery: windows on the life sciences*. Oxford: Blackwell Science. p. 4. ISBN 0-632-04452-7.

67 ^ Mazur, R.H. (1984). "Discovery of aspartame". In *Aspartame: Physiology and Biochemistry*. L. D. Stegink and L. J. Filer Jr. (Eds.). Marcel Dekker, New York, pp. 3–9.

68 ^ "Torunn A. Garin, 54, Noted Food Engineer". *The New York Times*. 1 May 2002.

69 ^ Testimony of Dr. Adrian Gross, Former FDA Investigator to the U.S. Senate Committee on Labor and Human Resources, 3 November 1987. Hearing title: "NutraSweet Health and Safety Concerns." Document # Y 4.L 11/4:S.HR6.100, page 430–439.

70 ^ FDA Statement on Aspartame, 18 November 1996

71 ^ British Pharmacopoeia Commission Secretariat. "Index (BP)" (PDF). Archived from the original (PDF) on 11 April 2009. Retrieved 16 January 2010.

72 ^ United States Pharmacopeia. "Food Ingredient Reference Standards" (PDF). Archived from the original (PDF) on 31 March 2010. Retrieved 16 January 2010.

73 ^ J.W. Childs Equity Partners II, L.P Archived 14 May 2007 at the Wayback Machine., *Food & Drink Weekly*, 5 June 2000

74 ^ Shapiro, Eben (19 November 1989). "Nutrasweet's Bitter Fight". *The New York Times*.

75 ^ "Ajinomoto May Exceed Full-Year Forecasts on Amino Acid Products – Bloomberg". Bloomberg. 18 November 2004. Retrieved 23 June 2010.

76 ^ "Sweetener sale-05/06/2000-ECN". icis.com. Retrieved 9 July 2010.

77 ^ "Asda gears up for additives battle/ aspartame". *Evening Standard*. London. Retrieved 23 June 2010. “This is Money”

78 ^ "Asda claims victory in aspartame 'nasty' case". foodanddrinkeurope.com. Retrieved 23 June 2010.

79 ^ "FoodBev.com". foodbev.com. Retrieved 23 June 2010. “Court of Appeal rules in Ajinomoto/Asda aspartame case”

80 ^ "Radical new twist in Ajinomoto vs Asda 'nasty' battle". foodnavigator.com. Archived from the original on 6 June 2010. Retrieved 23 June 2010.

81 ^ Bouckley, Ben (18 May 2011). "Asda settles 'nasty' aspartame legal battle with Ajinomoto". William Reed Business Media SAS. FoodNavigator.com. Retrieved 18 July 2011.

82 ^ "Ajinomoto brands aspartame AminoSweet". Foodnavigator.com. 25 November 2009. Retrieved 7 July 2010.

- "Ajinomoto brands aspartame 'AminoSweet'". FoodBev.com. 17 November 2009. Retrieved 7 July 2010.

83 **^** Lee, Thomas D. (2007). "Sweetners". *Kirk-Othmer Encyclopedia of Chemical Technology*. **24** (5th ed.). Wiley. pp. 224–252. ISBN 0-471-48496-2. doi:10.1002/0471238961.19230505120505.a01.pub2.

84 **^** "Holland Sweetener rolls out Twinsweet". *BakeryAndSnacks.com*. William Reed Business Media. 19 November 2003. Retrieved 29 July 2011.

85 **^** "Holland Sweetener Company to exit from aspartame business" Archived 7 May 2013 at the Wayback Machine.. DSM press release, U.S. Securities and Exchange Commission. 30 March 2006.

86 **^** Warner, Melanie (22 December 2004). "A Something Among the Sweet Nothings; Splenda Is Leaving Other Sugar Substitutes With That Empty Feeling". *The New York Times*.

87 **^** John Schmeltzer (2 December 2004). "Equal fights to get even as Splenda looks sweet". *Chicago Tribune*. Retrieved 4 July 2007.

88 **^** Carney, Beth (19 January 2005). "It's Not All Sweetness for Splenda". *BusinessWeek: Daily Briefing*. Archived from the original on 7 October 2008. Retrieved 5 September 2008.

89 **^** "Aspartame defence courts reaction". beveragedaily.com. 7 October 2004.

90 ^ Jump up to:
[a] [b] Mikkelson, David (August 12, 2014) The worlds best anti poison. Snopes.com

91 **^** Spoof news: FDA certifies Aspartame as ant poison. TheSpoof.com (12 August 2006)