

Aspartame

Aspartame is an artificial sweetener found in more than 6,000 products used by more than 200 million people worldwide. The typical consumption is 2-3 mg/kg/day, but can be much higher.

Aspartame passed the human and the animal data screens, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee (CIC) for consultation¹. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data (four additional studies identified since consultation in 2009)

- Cohort studies
 - Prospective study of aspartame consumption in beverages and hematopoietic and brain malignancies in >400,000 men and women ages 51-70 in the US National Institutes of Health-AARP Diet and Health Study): Lim *et al.* (2006)
 - *No significant associations with overall hematopoietic cancer, glioma, or their subtypes*
 - * Prospective study of aspartame consumption in soda and hematopoietic cancers in 77,218 women from the Nurses' Health Study and 47,810 men from the Health Professionals Follow-Up Study in the US: Schernhammer *et al.* (2012)
 - *Increased risk for non-Hodgkin lymphoma in men in the highest quartile of aspartame intake (Risk Ratio (RR)=1.64 [95% Confidence Interval (CI): 1.17–2.29]) with significant dose-response trend*
 - *Increased risk for multiple myeloma in men in the highest quartile (RR=3.36 [95% CI: 1.38–8.19]) and in the next highest quartile (RR=2.96 [95% CI: 1.25–6.96]) with the p value for trend = 0.05*
 - *No significant associations of aspartame intake with hematopoietic cancers were observed for women, or for the two cohorts combined.*
 - * Prospective study of artificially and sugar-sweetened carbonated beverage consumption and lymphoid neoplasms in 100,442 men and women (average age 69.2 years) from the Cancer Prevention Study-II Nutrition Cohort in the US: McCullough *et al.* (2014)
 - *Increased risks observed for all non-Hodgkin lymphoma (including multiple myeloma), all non-Hodgkin lymphoma (excluding multiple myeloma), and diffuse large B-cell lymphoma (a subtype of non-Hodgkin lymphoma) in Quintile 2 (median aspartame intake 3.6 mg/d) and Quintile 3 (median aspartame intake 12.6 mg/d) of aspartame intake. RRs for diffuse large B-cell lymphoma were 1.82*

¹ Aspartame passed the animal data screen in 2009 and was brought to the CIC for consultation. At that time the CIC recommended that aspartame be placed at the bottom of the 'medium' priority group for development of hazard identification materials. Since 2009, additional epidemiology data, animal cancer bioassays, and genotoxicity data have become available. Studies identified since prioritization and consultation with the CIC in 2009 are marked with an asterisk (*).

[95%CI: 1.22–2.72] and 1.62 [95%CI: 1.07–2.45] for Quintile 2 and 3, respectively. No dose-response trends observed.

- Case-control studies
 - * Population-based case-control study of brain cancer in subjects aged 19 or younger in the US: Gurney *et al.* (1997)
 - No association between aspartame consumption and pediatric brain cancer
 - Integrated analysis of several case-control studies of various cancers and aspartame consumption in four areas of Italy: Gallus *et al.* (2007)
 - No association between consumption of sweeteners other than saccharin (e.g., primarily aspartame) and cancers of the oral cavity, pharynx, esophagus, colon, rectum, larynx, breast, ovaries, prostate, or kidney
 - * Hospital-based case-control study of brain cancer in France: Cabaniols *et al.* (2011)
 - No association between aspartame intake (>once per week) and “malignant primitive brain tumors”
- Ecological studies
 - Time-related studies of brain tumor incidence and consumption of aspartame: Roberts (1991), Olney *et al.* (1996)
 - Studies point to temporal association between introduction of aspartame as an artificial sweetener and increase in incidence of certain brain tumors

Animal carcinogenicity data (four additional sets of studies identified since consultation in 2009)

- Long-term feed studies in mice
 - * Two-year studies in male and female ICR Swiss mice: G.D. Searle Carcinogenicity Bioassays E-75² (1974), as reviewed in Soffritti *et al.* (2014, pp. 387-388)
 - No treatment-related tumor findings
 - * Transplacental plus lifetime exposure studies in male and female Swiss mice (exposure started on gestation day 12 and continued through lactation, and via feed from weaning till death): Soffritti *et al.* (2010)
 - Increases in hepatocellular adenoma (by trend), hepatocellular carcinoma (by pairwise comparison and trend), combined hepatocellular adenoma and carcinoma (by pairwise comparison), and lung alveolar/bronchiolar carcinoma (by trend) in males
 - No treatment-related tumor findings in females

² E-75 is one of the three sets of two-year carcinogenicity bioassays submitted to the US Food and Drug Administration (FDA) by G.D. Searle, the manufacturer. These studies were not published in the peer-reviewed scientific literature; however, the final study reports are available on the European Food Safety Authority's (EFSA) website at <http://www.efsa.europa.eu/en/dataclosed/call/110601>, following EFSA's call for data on aspartame.

- Long-term feed studies in rats
 - Two-year studies in male and female Charles River Ceasarean Derived (CD) Sprague-Dawley rats: Searle Laboratories (1973), also known as G.D. Searle Carcinogenicity Bioassays E-33/34³, as reviewed in US FDA (1981, pp. 38298-38300)⁴, Olney *et al.* (1996)⁵, and Soffritti *et al.* (2014, p. 384 and p. 387)
 - *Possible increase in brain tumors (not statistically significant) in males*
 - *Possible increase in brain tumors (by Cox and Breslow trend tests) in females*
 - * Transplacental plus two-year exposure studies in male and female Charles River Ceasarean Derived (CD) Sprague-Dawley rats: G.D. Searle Carcinogenicity Bioassays E-70⁶ (1974), as reviewed in Soffritti *et al.* (2014, p. 387) and US FDA (1981)
 - *No treatment-related tumor findings*
 - * Two-year study in male SCL Wistar rats: Ishii (1981); Ishii *et al.* (1981)
 - *No treatment-related tumor findings*
 - Lifetime studies in male and female Sprague-Dawley rats (exposure started at 8 weeks of age): Soffritti *et al.* (2006), Soffritti *et al.* (2005), and Belpoggi *et al.* (2006)
 - *Increases in lymphomas/leukemias and peripheral nerve malignant schwannomas (each by trend) in males*
 - *Increases in lymphomas/leukemias (by pairwise comparison and trend), papillomas of the renal pelvis and ureter (by trend), and transitional cell carcinomas of renal pelvis and ureter (by pairwise comparison and trend) in females*
 - Transplacental plus lifetime exposure studies in male and female Sprague-Dawley rats (exposure started on gestation day 12 and continued through lactation, and via feed from weaning until death): Soffritti *et al.* (2007)
 - *Increase in lymphomas/leukemias (by author's Cox regression analysis) and occurrence of mammary carcinoma in treated males*
 - *Increases in lymphomas/leukemias and mammary carcinoma (by pairwise comparison and trend) in females*

³ E-33/34 is one of the three sets of two-year carcinogenicity bioassays submitted to the FDA by G.D. Searle, the manufacturer. These studies were not published in the peer-reviewed scientific literature; however, the final study reports are available on EFSA's website at <http://www.efsa.europa.eu/en/dataclosed/call/110601>, following EFSA's call for data on aspartame.

⁴ The FDA conducted its own independent examination of the pathology slides, and reported finding 13 brain tumors, with one in the controls and 12 in the treated groups.

⁵ Olney *et al.* (1996) mentioned that members of the Public Board of Inquiry (PBOI) panel, convened by the FDA in 1980, independently examined the records and histological slides and found that most of the tumors in aspartame-fed rats were gliomas (primarily astrocytic) and 8 out of 12 were so large that they could be detected by gross inspection. These tumors were also early onset and appeared to be rapidly growing.

⁶ E-70 is one of the three sets of two-year carcinogenicity bioassays submitted to the FDA by G.D. Searle, the manufacturer. These studies were not published in the peer-reviewed scientific literature; however, the final study reports are available on EFSA's website at <http://www.efsa.europa.eu/en/dataclosed/call/110601>, following EFSA's call for data on aspartame.

Other relevant data (several additional studies identified since consultation in 2009)

- Genotoxicity: as reviewed in EFSA (2013, pp. 59-63 and Appendix H, pp. 207-214), unless otherwise noted
 - *In vitro*:
 - Mutations
 - In *Salmonella typhimurium*
 - In TA97 (*negative and equivocal*⁷)
 - In TA98, TA100, TA1535, TA1537, and TA1538 (*negative with and without exogenous activation*)
 - In *Escherichia coli* with phenylalanine (an aspartame metabolite): Sargentini and Smith (1986)
 - In *wild-type, uvrB umuC, and uvrB lexA* strains (*negative*)
 - In *uvrB* strain (*positive*)
 - * DNA binding in calf thymus DNA: Kashanian *et al.* (2013) (*positive*)
 - Micronucleus formation in cultured human lymphocytes (*positive without exogenous activation*)
 - Unscheduled DNA synthesis in primary rat hepatocytes (*negative*)
 - Chromosomal aberrations (CA) in human lymphocytes (*positive without exogenous activation*)
 - Somatic segregation (resulting in haploid segregants and mitotic recombination) in diploid *Aspergillus nidulans*: Gebara *et al.* (2003) (*positive*)
 - Sister chromatid exchanges in cultured human lymphocytes (*negative without exogenous activation*)
 - *In vivo*:
 - DNA damage (Comet assay)
 - In bone marrow cells of Swiss albino mice (*positive*)
 - In stomach, colon, liver, kidney, bladder, lung, brain, and bone marrow of ddY mice (*negative*)
 - Micronucleus formation
 - * In bone marrow and peripheral blood cells of Swiss albino mice: Kamath *et al.* (2010) (*positive*)
 - In peripheral blood of transgenic mice (*negative*)
 - In bone marrow erythrocytes of Fischer 344/N rats (*negative*)
 - * DNA fragmentation in liver of both mother and offspring albino rats: Abd Elfatah *et al.* (2012) (*positive*)
 - CA
 - * In bone marrow of Swiss albino mice: Alsuhaibani (2010) (*positive*)

⁷ A reproducible small increase with 30% rat liver S9 was observed in one study.

- * In bone marrow of Swiss albino mice: Kamath *et al.* (2010) (*positive*)
- In rats
 - In bone marrow of Purina CD rats (*negative*)
 - In bone marrow and spermatogonial cells of Holtzman rats (*negative*)
 - * In bone marrow of both mother and offspring albino rats, and in liver of offspring: Abd Elfatah *et al.* (2012) (*positive*)
- Dominant lethal assay in Charles River CD rats (*negative*)
- Host-mediated assay
 - In Sprague-Dawley Ha/ICR Swiss mice with G-46 *Salmonella typhimurium* (*negative*)
 - In Purina CD rats with G-46 *Salmonella typhimurium* (*negative*)
- Metabolism
 - Aspartame is metabolized to formaldehyde, a known carcinogen: Soffritti *et al.* (2006); Magnuson *et al.* (2007)

Reviews

- EFSA (2013)

References

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