CENTER FOR Science IN THE Public Interest

Aspartame and Cancer: What is the Evidence?

Aspartame is an artificial sweetener used in thousands of products worldwide.[1] Questions about a possible link between aspartame and cancer have persisted for decades. However, compelling evidence now indicates that aspartame is a carcinogen. This fact sheet summarizes the evidence on aspartame and cancer, including important new evidence, and makes recommendations.

Animal Evidence

- The FDA relied on unpublished industry studies and others that reported no evidence of cancer[2,3] when it approved aspartame in 1981.[4] These studies used smaller numbers of animals than are now recommended by the FDA and other agencies, rendering them less able to detect cancers than larger studies.[5] Furthermore, female animals given the highest dose of aspartame in one study had significantly lower survival rates than controls, making the study less likely to detect tumors induced by aspartame.[6] Similarly, a very small 2005 government study piloting a new testing approach using transgenic mice[7] reported no excess cancer in aspartame-treated animals, but the government acknowledged the study might lack the sensitivity to detect cancer.[8]
- More recently, three independent, high-quality, peer-reviewed studies found that aspartame causes cancers in laboratory animals**.** That these cancers occur in multiple species, both sexes, and at multiple sites provides strong evidence that aspartame poses a cancer risk to humans. (The types of cancers reported in animal studies frequently vary depending on the conditions of the studies (e.g., timing of exposures, species, sex), including for known carcinogens).[9]
    - A 2006 rat study[10] reported that females treated with aspartame had statistically significant[11] increases in lymphomas/leukemias (L/L) and a very rare type of urinary tract cancer (transitional cell carcinomas of the renal pelvis/ureter) and related precancerous changes compared to untreated controls; and statistically significant dose-response trends in incidence of these and other tumors (in peripheral nerves, and malignant tumors overall) in one or both sexes.
        - This "mega-experiment" was better at detecting tumors than previous studies because it used many more animals and exposed them for a longer portion of their lifespans.[12]
        - Transitional cell carcinomas of the renal pelvis/ureter are so extremely rare in untreated rats of this strain, and thus highly unlikely to be due to chance.[13] Such rare tumors in a single animal study can be enough to conclude that an agent is likely carcinogenic to humans.[14]
    - A 2007 study[15] in which rats were dosed starting before birth (prenatally) also reported statistically significant[16] increases in L/L in treated males and females and in mammary (breast) cancers in females compared to untreated controls.
        - Exposures to aspartame begun prenatally produced much greater increases in L/L, and at earlier ages, than postnatal exposures only[17,18] – a finding raising special concerns for consumption of aspartame by pregnant women.
    - A 2010 study[19] in which mice were administered aspartame beginning prenatally reported statistically significant[20] increases in hepatocellular (liver) carcinomas and alveolar-bronchiolar (lung) carcinomas in treated males vs. controls.
- Diagnoses of L/L in the 2006 rat study were generally confirmed by pathologists[21] convened by the National Institute of Environmental Health Sciences (NIEHS) to provide a "second opinion" about cancers in the 2006 rat study, at the request of the authors of the study.
- After questions were raised about the independent laboratory's accuracy in diagnosing L/L in rats ,[22] a 2020 study using state-of-the-art diagnostic methods confirmed most (92%) L/L diagnoses in the 2007 prenatal rat study and the occurrence of the L/L remained statistically significant.[23,24]

The Independent Laboratory Testing Aspartame Produces Valid Results

Although no stranger to controversy,[25] the independent laboratory that conducted the 2006, 2007, and 2010 studies described above—the Ramazzini Institute (RI) based in Bologna, Italy—has been assessed by scientists at several US regulatory agencies. Chemicals tested for carcinogenicity by both RI and the U.S. National Toxicology Program NTP) produce "remarkably consistent" results, according to an analysis by an NTP scientist.[26] A 2010 NTP review of RI found "very organized and clean facilities" and "meticulous detail to the necropsy recording, collecting, and archiving of materials/tissues." The review also found RI procedures and records "were within GLP [Good Laboratory Practice] expectations."[27] A 2011 NTP/Environmental Protection Agency (EPA)-sponsored review found "good agreement" between RI's and its own diagnoses for several cancers, but it diagnosed fewer L/L than did RI.[28] As previously noted, better diagnostic methods have now confirmed most of the L/L in the 2007 prenatal study.[29] A review of RI studies by EPA scientists concluded that "aspects of the RI design, including gestational exposure, lifespan observation, and larger numbers of animals and dose groups, may impart advantages that provide chemical risk assessors with valuable insights … not obtained from other bioassays."[30]

Human Evidence

- A 2012 prospective cohort study[31] reported a statistically significant[32] association between diet soda and total aspartame intake and risk of non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) in men. These cancers are very similar to the most frequently observed cancers (L/L) in the RI rat studies—thus providing additional supportive evidence that aspartame is a carcinogen. This study is arguably the best of the human studies, since it was the largest prospective study that considered long-term exposure to aspartame (22 years), and the only one that assessed exposure to aspartame over time, although all cohort studies, by their nature, have important limitations.
- Two other prospective studies did not report an association between aspartame and cancer, but they had shortcomings compared to the 2012 study. A large 2006 study[33] only evaluated older adults (ages 50 to 71), who could not have consumed aspartame until middle-age or older, given that aspartame was only approved in 1981. In addition, participants were followed for only five years and intakes of aspartame were modest (only about 16% consumed more than about one 12-ounce soda per day). A 2014 study[34] was smaller and followed participants for less time (10 years) than the 2012 study. Both the 2006 and 2014 studies assessed exposure to aspartame only when people entered the study, so they did not capture changes in consumption over time.

Biological Plausibility[35]

- Methanol, a breakdown product of aspartame, is metabolized in humans and rats to formaldehyde.[36] Formaldehyde is listed in the U.S. Report on Carcinogens as "known to be a human carcinogen,"[37] in part because it causes leukemia in humans.[38]
- Other chemicals that break down in the body to formaldehyde, including methanol and methyl tert-butyl ether (MTBE), are also linked to L/L.[39,40]
- An association between aspartame and L/L has been observed in female rats and male humans, as previously noted. Both have higher levels of an enzyme that converts methanol (a breakdown product of aspartame) to formaldehyde than do male rats and female humans.[41,42,43]
- Ingestion of alcoholic beverages inhibits the metabolism of methanol to formaldehyde. In the 2012 human study (above), in men consuming <u>at least</u> 2 diet sodas a day, those consuming less alcohol had a significantly higher risk of non-Hodgkin lymphoma than those with higher alcohol consumption.

Conclusions and Recommendations

The evidence that aspartame causes cancer[44] is compelling. The U.S. Report on Carcinogens considers an agent "Reasonably Anticipated To Be a Human Carcinogen" in several circumstances, including when "there is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors … in multiple species or at multiple tissue sites … or … to an unusual degree..."[45] Aspartame meets those criteria (but has not been reviewed in the Report). It causes statistically significant increases in tumors in multiple species *and* at multiple tissue sites *and* to an unusual degree (e.g., extremely rare urinary tract cancers). Limited human and mechanistic data support that conclusion.

Aspartame is potent (it caused a high incidence of tumors at both high and low dosages).[46]

By law, the Food and Drug Administration (FDA) cannot approve a food additive if it is found to induce cancer in animals or humans.[47]

The Center for Science in the Public Interest therefore recommends that:

- the FDA and authorities in other nations take immediate steps to withdraw approval of aspartame.
- all consumers avoid aspartame, especially pregnant women and children.
- the International Agency for Research on Cancer (IARC) review the cancer evidence on aspartame as soon as possible. (IARC has already designated aspartame a "high priority" for review,"[48] following CSPI's nomination.)
- companies reformulate their products to eliminate aspartame and use available, safer alternatives.

For more information, please contact the Center for Science in the Public Interest at policy@cspinet.org.

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[1] Calorie Control Council. *Aspartame*. July 14, 2009. https://caloriecontrol.org/aspartame/.
[2] Three unpublished studies by Ajinomoto and Nutrasweet, available from European Food Safety Authority. *Call for Scientific Data on Aspartame (E 951).* May 31, 2011. See E70 (Two Year Toxicity Study in the Rat (Final Report)); E33/34 (Lifetime Toxicity Study in the Rat (Final Report and Appendix)); E75 (104-Week Toxicity Study in the Mouse (Final Report)). https://www.efsa.europa.eu/en/consultations/call/110531.
[3] Ishii H. Incidence of Brain Tumors in Rats Fed Aspartame. *Toxicol Lett*. 1981;7:433-437. A Histopathological Re-evaluation Performed at Request of Ajinomoto. Original study (not a cancer bioassay) at Ishii H, et al. Toxicity of Aspartame and its Diketopiperazine for Wistar Rats by Dietary Administration for 104 Weeks. *Toxicology*. 1981;21(2):91-94.
[4] 46 Fed Reg. 142:38285. Aspartame: Commissioner's Final Decision.
[5] U.S. Food and Drug Administration. *Redbook 2000: IV.C.6. Carcinogenicity Studies with Rodents*. 2006. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/redbook-2000-ivc6-carcinogenicity-studies-rodents. The Redbook states, "It is recommended that carcinogenicity studies begin with at least 50 animals per sex per group." U.S. Environmental Protection Agency. *Guidelines for Carcinogen Risk Assessment.* 2005. https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf. The Guidelines state, "Current standardized carcinogenicity studies in rodents test at least 50 animals per sex per dose group in each of three treatment groups and in a concurrent control group" and cites the Organization for Economic Cooperation and Development (OECD). However, the two original industry rat studies used 40 rats/sex/group plus 60 controls, and the mouse study used 36 mice/sex group plus 72 controls. The 2005 NTP study in transgenic mice used 15 animals/sex/group. The Ishii 1981 study only examined brain tumors, using an Ishii et al 1981 study that was not a cancer bioassay.
[6] Soffritti M, et al. The Carcinogenic Effects of Aspartame: The Urgent Need for Regulatory Re-evaluation. *Am J Ind Med*. 2014;57(4):383-397.
[7] U.S. Department of Health and Human Services, National Toxicology Program. *NTP Report on the Toxicology Studies of Aspartame (CAS No. 22838-47-0) in Genetically Modified (FVB Tg.AC hemizygous) and B6.129-Cdkn2a^{tm1Rdp} (N2) Deficient Mice and Carcinogenicity Studies of Aspartame in Genetically Modified [B6.129-Trp53^{tm1Brd} (N5) Haploinsufficient] Mice (Feed Studies).* 2005. https://ntp.niehs.nih.gov/ntp/htdocs/gmm_rpts/gmm1.pdf.
[8] U.S. Department of Health and Human Services, National Toxicology Program. NTP Report states, "there is uncertainty whether the study possesses sufficient sensitivity to detect a carcinogenic effect."
[9] U.S. Department of Health and Human Services, National Toxicology Program. *Cancer Evaluation Criteria.* September 26, 2019. https://ntp.niehs.nih.gov/whatwestudy/testpgm/cartox/criteria/index.html. It is not unusual for cancers to vary depending on species, route or timing of exposure, or other conditions. The National Toxicology Program notes that positive results, "demonstrate that a chemical is carcinogenic for laboratory animals *under the conditions of the study* [emphasis added] and indicate that exposure to the chemical has the potential for hazard to humans." For example, women exposed to the drug diethylstilbestrol (DES) during pregnancy have an increased risk of breast cancer, and their daughters have an increased risk of cervical/vaginal cancer, according to the National Cancer Institute.
[10] Soffritti M, et al. First Experimental Demonstration of the Multipotential Carcinogenic Effects of Aspartame Administered in the Feed to Sprague-Dawley Rats. *Environ Health Perspect*. 2006;114(3):379-385.
[11] Lymphomas/leukemias: positive trend in males ($p \leq 0.05$) and females ($p \leq 0.01$); increases in females compared with controls at five doses tested (all except the lowest dose), ($p \leq 0.01$ at three doses, $p \leq 0.05$ at two doses). Carcinoma of renal pelvis/ureter: positive trend in females ($p \leq 0.05$); increases in females treated at 100,000 ppm ($p \leq 0.05$) compared with controls. Dysplastic lesions + carcinomas of renal pelvis/ureter: positive trend in females ($p \leq 0.01$); increases compared with controls at five dose tested (all except the lowest dose), ($p \leq 0.01$ at three doses and $p \leq 0.05$ at two doses). A 3-fold increase was observed at the lowest dose (80 ppm). Malignant schwannomas of peripheral nerves in males: positive trend ($p \leq 0.05$). Malignant tumors overall: positive trend in males ($p \leq 0.05$) and females ($p \leq 0.01$); increases in females at 50,000 ppm ($p \leq 0.01$) vs. controls.
[12] The study used a control group plus six groups of laboratory rats, 100-150 animals/sex/group, and dosages in feed ranging from 80 ppm to 100,000 ppm aspartame, from 8 weeks until natural death. The industry studies used 36-40 animals/dose group, 2-4 groups, plus 60-72 controls. See note 5.

Typically, carcinogenicity studies with rats use a control group plus three (occasionally five) groups, 50 animals/sex group, and are terminated after two-years.
[13] Transitional cell carcinomas of renal pelvis/ureter were found in 21/1500 aspartame treated animals vs. 0 in the concurrent controls (Soffritti et al, 2006). They were found in 0 historical controls for this laboratory (of 1,934 males and 1,945 females). In 17 studies using 2,669 control Sprague-Dawley rats, there were found in only 1 male and 1 female (*Toxicol Pathol.* 1991;19(3):287-289).
[14] U.S. Environmental Protection Agency. *Guidelines for Carcinogen Risk Assessment*. 2005. https://www3.epa.gov/airtoxics/cancer_guidelines_final_3-25-05.pdf.
[15] Soffriti M, et al. Lifespan Exposure to Low Doses of Aspartame Beginning During Prenatal Life Increases Cancer Effects in Rats. *Environ Health Perspect.* 2007;115:1293-1297.
[16] Lymphomas/leukemias: positive trend in females ($p \leq 0.01$); increases compared with controls at 2,000 ppm in females ($p \leq 0.01$) and males ($p \leq 0.05$). Mammary carcinomas: positive trend in females ($p \leq 0.05$); increases compared with controls at 2,000 ppm in females ($p \leq 0.05$).
[17] Soffriti M, et al. 2007.
[18] Landrigan PJ, Straif K. Aspartame and Cancer – New Evidence for Causation. *Environ Health.* 2021;20(1):42.
[19] Soffriti M, et al. Aspartame Administered in Feed, Beginning Prenatally Through Life Span, Induces Cancers of the Liver and Lung in Male Swiss Mice. *Am J Ind Med.* 2010;53(12):1197-1206.
[20] Hepatocellular carcinomas: positive trend in males ($p < 0.01$); increases compared with controls at two highest doses ($p < 0.01$ at 32,000 ppm, ($p < 0.05$ at 16,000 ppm). Alveolar/bronchiolar carcinomas: positive trend in males ($p < 0.05$); increases compared with controls at 32,000 ppm ($p < 0.05$).
[21] Hailey JR, Pathology Working Group Chair. National Institute of Environmental Health Sciences. *Pathology Working Group Chairperson's Report: Lifetime Study in Rats Conducted by the Ramazzini Foundation.* Submitted to Dr. Fiorella Belpoggi, Ramazzini Foundation. 2014.
[22] U.S. Environmental Protection Agency. *Update on Ramazzini Institute Data in IRIS Assessments.* n.d. https://www.epa.gov/iris/update-ramazzini-institute-data-iris-assessments.
[23] Tibaldi E, et al. Identification of Aspartame-Induced Haematopoietic and Lymphoid Tumours in Rats After Lifetime Treatment. *Acta Histochem*. 2020;122(5):15148.
[24] Landrigan PK, Straif K. 2021.
[25] Horel S, Foucart S. The Monsanto Papers, Part 1—Operation: Intoxication. *Environmental Health News.* November 20, 2017. https://www.ehn.org/monsanto-glyphosate-cancer-smear-campaign-2509710888/a-years-work-to-evaluate-the-pesticide.
[26] Huff J. Chemicals Studied and Evaluated in Long-Term Carcinogenesis Bioassays by both the Ramazzini Foundation and the National Toxicology Program: In Tribute to Cesare Maltoni and David Rall. *Ann NY Acad Sci.* 2002;982:208-230.
[27] Malarkey DE, Bucher JR. Summary Report of the National Toxicology Program and Environmental Protection Agency-Sponsored Review of Pathology Materials form Selected Ramazzini Institute Rodent Cancer Bioassays. 2011. https://ntp.niehs.nih.gov/ntp/about_ntp/partnerships/international/summarypwg_report_ri_bioassays.pdf.
[28] Malarkey and Bucher, 2011
[29] Tibaldi E, et al. 2020.
[30] Gift JS, et al. Scientific Considerations for Evaluating Cancer Bioassays Conducted by the Ramazzini Institute. *Environ Health Perspect*. 2013;12(11-12):1253-1263.
[31] Schernhammer ES, et al. Consumption of Artificial Sweetener- and Sugar-Containing Soda and Risk of Lymphoma and Leukemia in Men and Women. *Am J Clin Nutr*. 2012;96(6):1419-1428.
[32] In men, $\geq$1 daily serving of diet soda increased risks of non-Hodgkin lymphoma (NHL) (RR: 1.31; 95% CI: 1.01-1.72) and multiple myeloma (MM) (RR: 2.02; 95% CI: 1.20-3.4) compared to men who did not consume diet soda. For men and women combined, $\geq$1 daily serving of diet soda increased risk of leukemia (RR: 1.42; 95% CI: 1.00-2.02). For men in the highest quintile of aspartame intake, RRs were 1.64 (95% CI:1.17-2.29, *P*-trend = 0.002) for NHL, 3.36 (95% CI: 1.38-8.19, *P*-trend = 0.05 for MM.
[33] Lim U, et al. Consumption of Aspartame-Containing Beverages and Incidence of Hematopoietic and Brain Malignancies. *Cancer Epidemiol Biomarkers Prev*. 2006;15(9):1654-1659.
[34] McCullough ML, et al. Artificially and Sugar-Sweetened Carbonated Beverage Consumption is Not Associated with Risk of Lymphoid Neoplasms in Older Men and Women. *J Nutr*. 2014;144(12):2041-2049.
[35] Schernhammer ES, et al. 2012. States, "The potential carcinogenicity of aspartame is biologically plausible" and expands on these arguments.
[36] U.S. Department of Health and Human Services, National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction. *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Methanol*. September 2003. https://ntp.niehs.nih.gov/ntp/ohat/methanol/methanol_monograph.pdf. Also discussed in Soffriti M, et al. 2006.
[37] U.S. Department of Health and Human Services, National Toxicology Program. *14th Report on Carcinogens.* 2016. https://ntp.niehs.nih.gov/ntp/roc/content/profiles/formaldehyde.pdf.
[38] U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. *Formaldehyde.* February 14, 2019. https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/formaldehyde.
[39] Soffritti M, et al. Results of Long-Term Experimental Studies on the Carcinogenicity of Methyl Alcohol and Ethyl Alcohol in Rats. *Ann N Y Acad Sci*. 2002;982:46-69.
[40] Belpoggi F, Soffritti M, Maltoni C.Methyl-tertiary-butyl ether (MTBE) --a Gasoline Additive--Causes Testicular and Lymphohaematopoietic Cancers in Rats. *Toxicol Ind Health*. 1995;11(2):119-148.
[41] Simon FR, et al. Sexual dimorphic expression of ADH in rat liver: importance of the hypothalamic-pituitary-liver axis. *Am J Physiol Gastrointest Liver Physiol*. 2002;283(3):G646-G655.
[42] Soffriti M, et al. 2014.
[43] Schernhammer ES, et al. 2012.
[44] Most authorities assume that chemicals that cause cancer in animals cause cancer in humans, unless there is strong evidence otherwise. The U.S. Environmental Protection Agency states in its *Guidelines for Carcinogen Risk Assessment* (2006, p. 2-22) that "tumors observed in animals are generally assumed to indicate that an agent may produce tumors in humans." The International Agency for Research on Cancer states in its Preamble to the IARC Monographs on the Identification of Carcinogenic Hazards to Humans (2019), "it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals … present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, such as strong evidence that a given agent causes cancer in experimental animals through a species-specific mechanism that does not operate in humans … these agents are considered to pose a potential carcinogenic hazard to humans. The inference of potential carcinogenic hazard to humans does not imply tumour site concordance across species …."
[45] U.S. Department of Health and Human Services, National Toxicology Program. Report on Carcinogens Process & Listing Criteria. September 25, 2019. https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/criteria/index.html.
[46] Landrigan PK, Straif K. 2021.
[47] 21 U.S.C. §348(c)(3)(A). Food additives.
[48] World health Organization, International Agency for Research on Cancer. IARC Monographs on the Identification of Carcinogenic Hazards to Humans. *Report of the Advisory Group to Recommend Priorities for the IARC Mongraphs during 2020-2024*. 2019. https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf and *Report of the Advisory Group to Recommend Priorities for IARC Monographs during 2015-2019.* 2014. https://monographs.iarc.who.int/wp-content/uploads/2018/08/14-002.pdf.