foodwatch

Report 2025

CLEAN WASHING ASPARTAME

Why aspartame needs to be banned, based on independent science.

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KEY FINDINGS

- **Aspartame is found in 6,000+ Products worldwide:** Aspartame is used in thousands of products in the food and beverage industry, especially in diet and sugar-free items like Coca-Cola Zero or Pepsi Zero.

- In 2023, **IARC (the WHO's International Agency for Research on Cancer)** classified **aspartame as "possibly carcinogenic to humans"** (Group 2B), citing credible evidence of cancer risks from independent studies.

- **Heavy Reliance on Industry Studies by European Food Safety Authority (EFSA):** According to foodwatch's analysis **nearly three-quarters of EFSA's so-called reliable studies** on aspartame were funded or influenced by the industry, undermining the credibility of their risk assessments and thus of aspartame's approval.

- **Independent Research Demands Action:** Studies by the **Ramazzini Institute** and other independent bodies show dose-dependent carcinogenic effects in animal models, supporting the need for regulatory intervention.

- **Other Potential Health Risks:** Emerging research links aspartame to other health issues, including **cardiovascular diseases, type 2 diabetes, neurotoxicity,** and **negative effects on the gut microbiome**.

- **JECFA's (Joint FAO/WHO Expert Committee on Food Additives) 2023 conclusion** that aspartame does not pose a threat to consumers at current consumption levels **relied heavily on a single industry-funded study from 1981**, despite IARC findings. This study, conducted by the leading aspartame manufacturer, raises serious questions about transparency and credibility.

- foodwatch calls on the European Commission to **apply the precautionary principle and ban aspartame.** In case of scientific uncertainties about the potential harm of a substance, the precautionary principle allows regulators to take protective action.

If consumers are faced with the decision of whether to take cola with sweeteners or one with sugar, I think there should be a third option considered – which is to drink water instead.

Francesco Branca, WHO's head of Nutrition, 2023.
www.theguardian.com/society/2023/jul/13/aspartame-a-possible-carcinogen-but-safe-to-consume-in-moderation-who-says

1 INTRODUCTION

Imagine a sweetener widely celebrated as safe, embraced by the masses, and deemed a breakthrough for diabetics. For years, it is a symbol of progress – a better, healthier alternative to sugar. Then, gradually, it disappears, banned for posing unacceptable health risks. It sounds improbable, almost unthinkable, but this is the story of dulcin.

Discovered in 1884,[1] dulcin was a synthetic sweetener 250 times sweeter than sugar.[2] It enjoyed widespread use in the late 19th and early 20th centuries, hailed as a miracle for diabetics and a revolutionary alternative to sugar. For decades, it was considered both effective and safe. Yet by the mid-20th century, doubts began to emerge. Studies linked dulcin to liver and bladder cancer in animal tests, and toxic incidents further heightened alarm.[3] The United States (US) banned it in the early 1950s,[4] with Japan following in 1969.[5] In Europe, its use quietly ended as safety standards evolved. Today, hardly anybody remembers it even existed – and more importantly: Nobody misses it.

The story of dulcin is a stark reminder that substances initially hailed as innovative solutions can later be found to pose serious health risks. It underscores the importance of acting decisively when concerns become apparent, even if evidence remains incomplete. In hindsight, banning dulcin wasn't premature – it was essential and overdue. This example is illustrative of what European General Food Law calls the precautionary principle: when scientific evidence suggests potential harm, even without complete certainty, it is wiser to take action sooner rather than later. Lives can be at stake. The precautionary principle is a founding EU principle, enshrined in Article 191 of the Treaty on the Functioning of the European Union, which enables decision makers to adopt regulatory measures when scientific evidence

[1] Berlinerblau J (1884) Ueber die Einwirkung von Chlorcyan auf Ortho- und auf Para-Amidophenetol. Journal für praktische Chemie 30:97–115. doi:10.1002/prac.18840300110
[2] https://www.chemie.de/lexikon/dulcin.html
[3] https://www.inchem.org/documents/jecfa/jecmono/v44aje37.htm
[4] https://s3.amazonaws.com/archives.federalregister.gov/issue_slice/1950/1/19/317-324.pdf#page=5
[5] https://labchem-wako.fujifilm.com/asia/category/01816.html

about an environmental or human health hazard is inconclusive and the potential negative consequences are high. Today, as this report will argue, the precautionary principle demands the same decisive action for aspartame.

Aspartame, a sweetener found in approximately 6,000 products worldwide,[6] plays a significant role in the beverage industry, offering an option to avoid regulatory actions on sugar. Its safety has been a topic of heated debate for decades, and in 2023, this controversy was reignited following opinions by two international authorities: IARC (the WHO's International Agency for Research on Cancer) and JECFA (the Joint FAO/WHO Expert Committee on Food Additives). The two bodies reached apparently conflicting conclusions – while IARC classified aspartame as "possibly carcinogenic to humans", JECFA maintained that it poses no harm to consumers. In an unusual move, both organisations issued a joint statement that left the public more confused than reassured.[7] The following sections argue that the findings of IARC and independent research provide compelling grounds for a precautionary ban on aspartame.

Food products containing aspartame (Germany, January 2025).

[6] Magnuson BA, Burdock GA, Doull J, Kroes RM, et al. (2007) Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. Crit Rev Toxicol. 37(8):629-727. doi: 10.1080/10408440701516184

[7] https://www.who.int/news/item/14-07-2023-aspartame-hazard-and-risk-assessment-results-released

The report will unfold these arguments in the following steps:

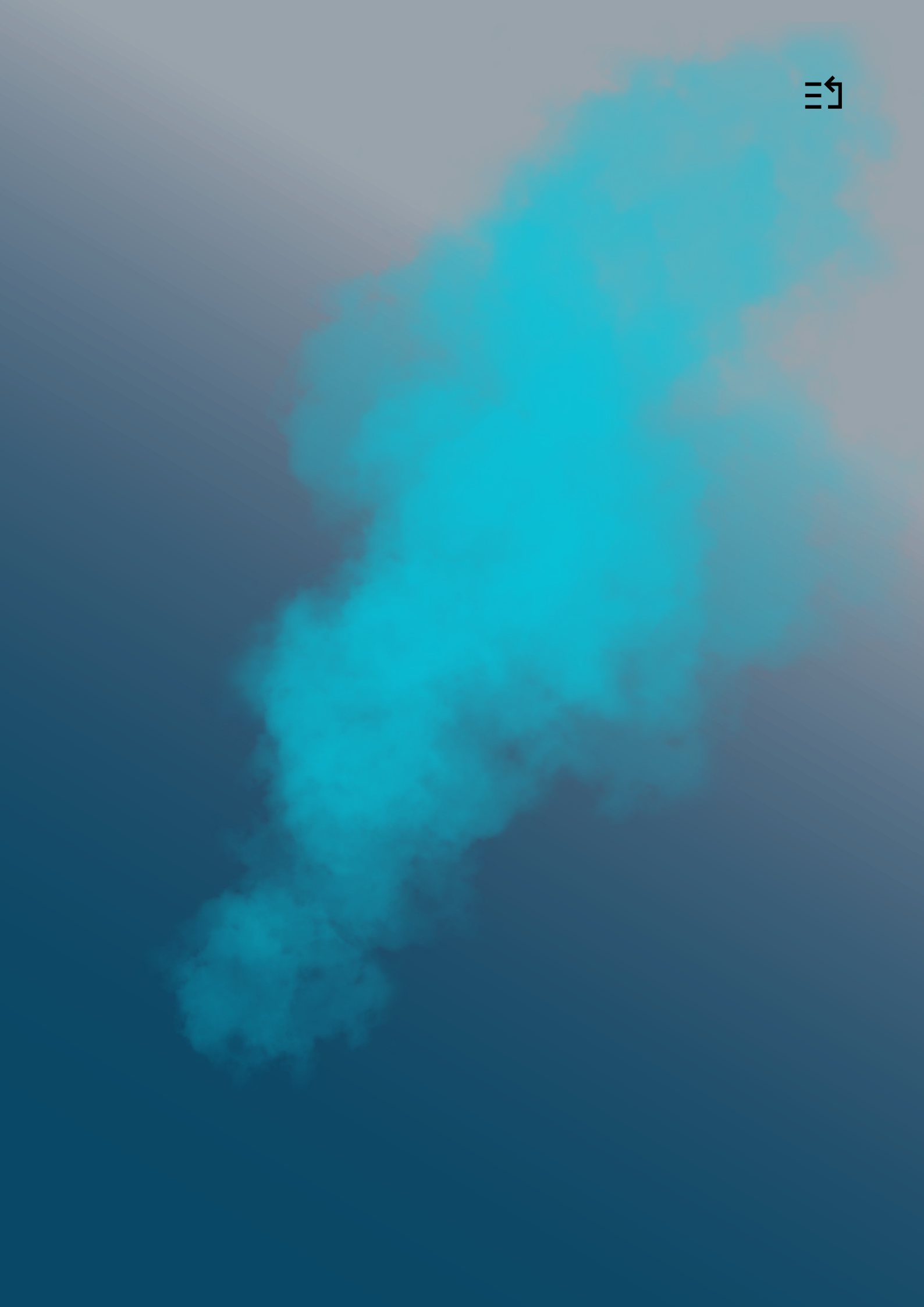
- Aspartame has become indispensable for the beverage industry, enabling profitability amid growing regulatory pressures like sugar taxes. Corporate interests overshadow mounting concerns about its safety. (Chapter 2)

- The regulatory approval of aspartame has been heavily influenced by industry-funded studies, raising concerns about bias and credibility. Flaws in these processes undermine public trust in the regulatory framework. (Chapter 3)

- Independent research has uncovered significant health risks linked to aspartame, including evidence of a possible role in cancer causation. Reflecting these concerns, IARC classified aspartame as "possibly carcinogenic to humans" with some panellists advocating for an even stricter classification. These findings directly challenge the industry's claims of safety and underscore the need for further investigation. (Chapter 4)

- By contrast, JECFA's 2023 evaluation of aspartame relies disproportionately on industry-backed data, ignoring independent research highlighting potential risks. (Chapter 5)

- The precautionary principle provides a clear legal basis for banning aspartame, as the credible evidence of health risks cannot be dismissed. Protecting public health must take precedence over industry interests. (Chapter 6)



2 ASPARTAME: AN INDUSTRY SUCCESS STORY

Aspartame is a low-calorie artificial sweetener widely used as a sugar substitute in foods and beverages. It is approximately **200 times sweeter than sugar**. Only small amounts are needed to achieve the desired sweetness.

Aspartame was discovered in 1965 by James M. Schlatter, a chemist at **G.D. Searle & Company**, while researching anti-ulcer medications. Its sweetness was accidentally noticed when Schlatter licked his fingers.[8] Due to controversies around its safety, its first approval as a food additive took almost two decades. The US Food and Drug Administration (FDA) approved it in 1983 for use in carbonated beverages and in 1993 for use in in other beverages, baked goods, and confections.[9]

Many consumers became familiar with aspartame through the brand **NutraSweet**, which gained prominence in the 1980s and 1990s. NutraSweet was widely used as a low-calorie sweetener in various products, and its presence was bolstered by extensive advertising campaigns.[10]

90's NutraSweet TV commercial, https://www.youtube.com/watch?v=EIoufRS-Ua0, screen shot from 07.01.2025

[8] https://www.washingtonpost.com/archive/lifestyle/food/1982/09/22/the-market-is-sweet-on-aspartame/104de9dd-ca6f-40ec-84a8-58166cf23585/

[9] https://www.fda.gov/food/food-additives-petitions/timeline-selected-fda-activities-and-significant-events-addressing-aspartame and; https://archives.federalregister.gov/issue_slice/1993/4/19/21095-21100.pdf

[10] https://www.encyclopedia.com/books/politics-and-business-magazines/nutrasweet-company

The global aspartame market today is controlled by a handful of dominant players. **Ajinomoto Group (Japan)** produces and markets aspartame under the name **AminoSweet. HSWT (France)** is a significant European supplier that serves the demands of the food and beverage industry.

2.1 ASPARTAME: THE WAY OUT FOR COKE & CO.

Aspartame is widely used today, supposedly in over 6,000 products worldwide. And the demand for aspartame is growing: The global market value for aspartame is projected to rise from USD 375.5 million in 2021 to USD 561.7 million by 2031, a growth of roughly 50% in only 10 years.[11]

The reason for that is simple: Since its discovery, aspartame has been eagerly adopted by the food and beverage industry as a tool to market "diet" and "light" products.[12] Most notably, it is widely used in drinks: Aspartame consumption is primarily linked to the intake of soft drinks, which account for approximately 95% of total aspartame consumption in all countries with foodwatch offices, including Austria, Belgium, France, Germany, and the Netherlands.[13]

Behind this is a notable shift in the soft drink industry: While the overall soft drink market in Europe stagnated between 2016 and 2021, there has been a significant increase in the market share of low- and no-calorie drinks, many of which rely on aspartame as a sugar substitute. These beverages have seen a rise in popularity, evolving from a niche product to a major segment of the soft drink market. Low- and no-calorie drinks were responsible for only 23% of total soft drink sales in 2016 but accounted for more than 40% by 2023.[14]

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[11] https://www.alliedmarketresearch.com/aspartame-market-A11795
[12] https://www.reuters.com/business/retail-consumer/pepsico-says-no-plans-change-portfolio-who-set-warn-aspartame-sweeteners-2023-07-13/
[13] Own calculations, based on Euromonitor data.
[14] Own calculations, based on UNESDA data.

Cover page of the Coca Cola Europacific Strategic report 2023: https://www.cocacolaep.com/assets/Global/Investors/Integrated-Report/2023-CCEP-Integrated-Report_Web-15.03.2024_v3-Interactive-Version-1.pdf

This shift is intentional: For example, Coca-Cola aims to derive over 50% of its sales in Europe from low or no-calorie drinks by 2025. To achieve this, it states that it will reduce the average sugar content in its beverages by reformulating existing products, such as Fanta Orange, and offering zero-calorie options alongside sugar-reduced variants.[15] PepsiCo, the other big soft drink player in Europe, has adopted a similar approach, setting targets to reduce the average level of added sugar in its EU soft drinks portfolio by 25% by 2025 and 50% by 2030. The company has already seen progress, with its no-sugar volume mix increasing by 5 points to reach 31% in 2021.[16] However, reliance on artificial sweeteners is unlikely to stem from a newly found commitment to public health. The industry's track record tells a different story. For instance, Coca-Cola has historically targeted children and teenagers with multi-million-dollar marketing campaigns while simultaneously lobbying against regulations like advertising bans or sugar taxes. The company has also funded research favouring industry interests – tactics that closely resemble those employed by the tobacco industry.[17]

[15] https://www.cocacolaep.com/assets/Global/Investors/Integrated-Report/2023-CCEP-Integrated-Report_Web-15.03.2024_v3-Interactive-Version-1.pdf p. 15-17
[16] https://food.ec.europa.eu/system/files/2022-05/f2f_sfpd_coc_report_2022_pepsico.pdf p. 2
[17] https://www.foodwatch.org/de/informieren/essen-gesundheit/zucker-fett-co/der-coca-cola-report

Manufacturers use aspartame to maintain the sweet flavour profiles of their products while reducing sugar content – a necessity in today's market. Over 130 countries now impose taxes on sugar-sweetened beverages,[18] with the majority of these measures introduced after 2010. For manufacturers, the appeal of aspartame is clear: it helps them sidestep regulatory pressures and avoid sugar taxes while maintaining the sweet taste for consumers.[19]

2.2 ASPARTAME IS A DRIVER OF PROFITS

Aspartame is not only a regulatory workaround for the beverage industry – it is also a highly cost-effective and profitable alternative to sugar.

Take the European aspartame market leader, HSWT, as an example. Based in Gravelines, France, this company supplies approximately a quarter of the EU's aspartame consumption while exporting a large share of its production.[20] Its market dominance has translated into impressive financial success: company revenues surged from EUR 34.3 million in 2020 to EUR 53.61 million in 2022, with a net margin of 7.13% in the latest fiscal year, but fell in 2023.[21]

For beverage manufacturers, aspartame offers an equally attractive advantage. Its extreme sweetness, 200 times that of sugar, requires only tiny quantities, significantly reducing production costs. Aspartame delivers equivalent sweetness at just one-tenth the price of sugar,[22] making it a highly efficient way to cut expenses while maintaining the appeal of their products. Yet, curiously, regular Coke and Coke "Zero Sugar" are sold at the same price[23] – a testament to how the industry leverages cost savings for profitability rather than passing them on to consumers.

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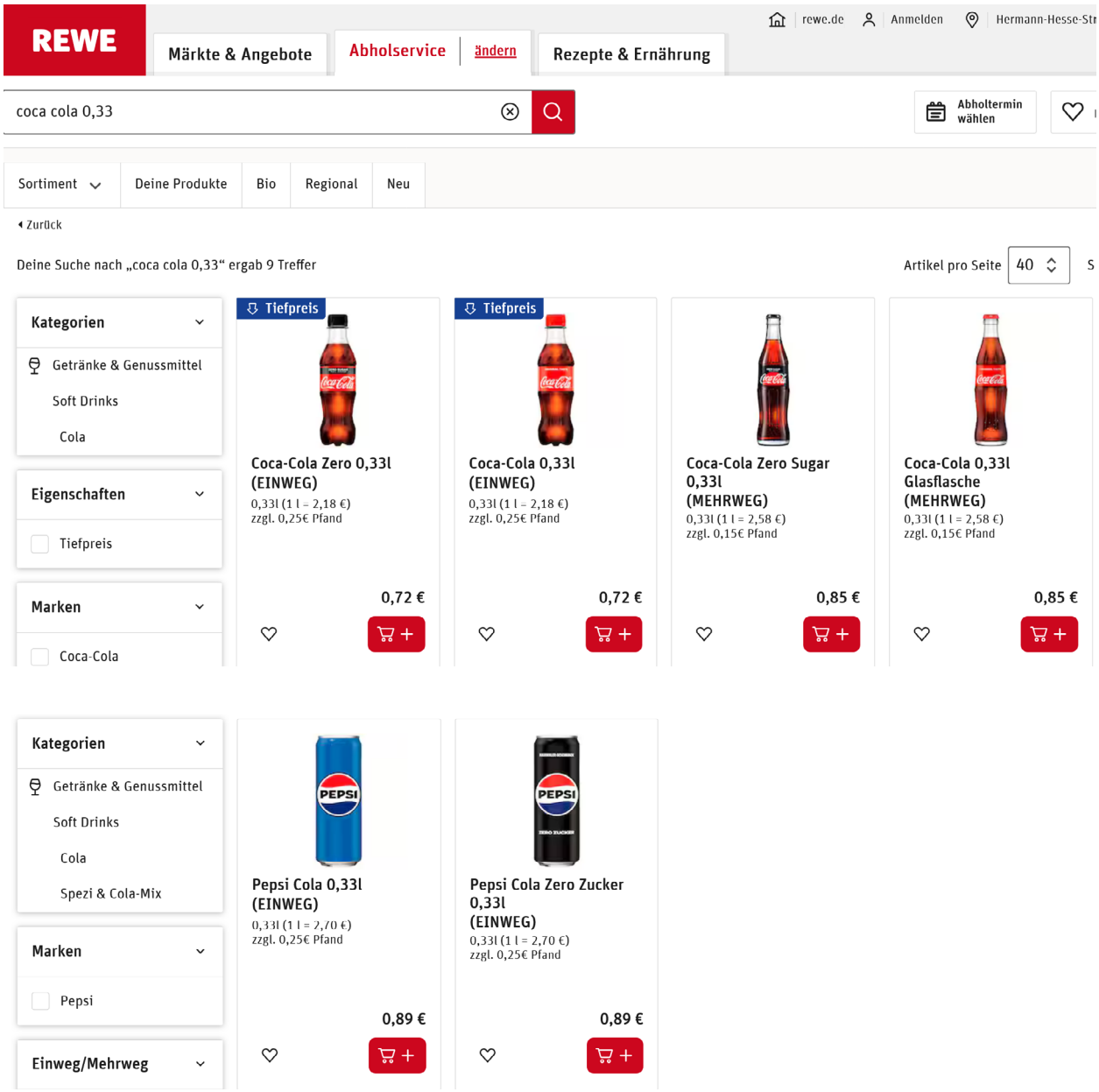
[18] https://ssbtax.worldbank.org/
[19] https://openknowledge.worldbank.org/server/api/core/bitstreams/4ca4b739-f713-5a89-aca2-02ec50976e7c/content p. 11
[20] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022R2001 p. 1,10, 30, 32
[21] https://www.societe.com/societe/hswt-france-844837070.html; https://infonet.fr/entreprises/84483707000029-hswt-france/
[22] Market prices: aspartame USD 10,49 per kg (https://www.imarcgroup.com/aspartame-pricing-report (Germany)), sugar USD 0,5 per kg (https://www.statista.com/statistics/675828/average-prices-sugar-worldwide/). Achieving same sweetness (aspartame 200x that of sugar) USD 0,5 for sugar and USD 0,05 for aspartame needed (calculation made on December 6, 2024).
[23] Own research, screen shots p. 11



Regular Coke and Pepsi Cola and "Zero Sugar" versions sold at the same price: https://shop.rewe.de/productList?search=%20coca%20cola%200%2C33%20&sorting=PRICE_ASC and https://shop.rewe.de/productList?search=pepsi%200%2C33&sorting=PRICE_ASC, screen shot from 24.01.2025

Looking at the industry influence on aspartame research in the next chapters, this is their vested interest behind it: Presenting aspartame as a safe and desirable ingredient allows them to cling to this substance to dodge regulations such as sugar taxes and advertising restrictions.

FIGHTING CRITICISM: HOW THE INDUSTRY DEFENDS ASPARTAME

A striking example of the aspartame industry's aggressive defence tactics is the 2008 lawsuit filed by Ajinomoto, a major aspartame producer, against British supermarket chain Asda. The dispute arose over Asda's "No Nasties" marketing campaign, which promoted the removal of artificial additives, including aspartame, from its own-brand products. Ajinomoto argued that labelling aspartame as "nasty" unfairly tarnished its reputation and misled consumers about the safety of the sweetener.

Asda product with "No Nasties" claim, https://groceries.asda.com/product/kids-yogurts-fromage-frais/the-collective-great-dairy-suckies-peach-apricot/1000383141825 Screen shot from 07.01.2025

While a UK High Court initially sided with Asda in 2009, stating that the "No Nasties" label did not imply aspartame was harmful, the Court of Appeal overturned this decision in 2010, allowing Ajinomoto to proceed with its claim. The case ultimately settled out of court in 2011, with Asda agreeing to remove references to aspartame from its packaging. This case highlights the industry's willingness to take legal action to defend its products and control public perception, ensuring that criticism of aspartame remains muted in the marketplace.[24, 25]

[24] https://www.independent.co.uk/news/uk/home-news/asda-wins-fight-over-nasty-sweetener-1747827.html

[25] https://www.foodnavigator.com/Article/2011/05/18/Asda-settles-nasty-aspartame-legal-battle-with-Ajinomoto/

3 CRITICISM IGNORED: HOW ASPARTAME SECURED ITS PLACE

- Aspartame was approved by major regulatory bodies, such as the US Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), largely based on industry-funded studies that were not peer-reviewed.
- The EU approval process for aspartame contained several loopholes, allowing the industry to push through favourable outcomes without sufficient scrutiny.
- Numerous studies and statements supporting aspartame's safety have been financed by the industry, raising concerns about the impartiality and credibility of such studies.

This chapter examines how regulatory authorities in the US and European Union (EU) handled aspartame's market entry and long-term pass. Particular attention is given to the European Food Safety Authority's (EFSA) 2013 re-evaluation process, which was marked by inconsistencies, industry influence, and links between panel members and industry groups.

3.1 ASPARTAME'S ROCKY START: THE FDA'S BACK-AND-FORTH

The very first approval process for aspartame was fraught with controversy, serving as an early warning of the safety concerns that would later return. Aspartame was first approved by the US Food and Drug Administration (FDA) in 1974 after manufacturer G.D. Searle submitted a series of safety studies.[26] The FDA is the central authority in the USA for the regulation and monitoring of food.[27] However, shortly afterwards, in 1975, the FDA suspended approval due to concerns about the quality of the studies submitted.[28] Some external scientists raised concerns about health risks[29] and

[26] https://archives.federalregister.gov/issue_slice/1974/7/26/27316-27320.pdf#page=2 p.27320-27320
[27] https://www.fda.gov/about-fda/what-we-do
[28] https://archives.federalregister.gov/issue_slice/1975/12/5/56899-56910.pdf#page=9 p. 56907
[29] Millstone EP, Dawson E (2019) EFSA's toxicological assessment of aspartame: was it even-handedly trying to identify possible unreliable positives and unreliable negatives? Arch Public Health. 77:34. doi: 10.1186/s13690-019-0355-z p. 3

Foto credit: Adobe Stock image, from PeskyMonkey

internal FDA reviewers discovered flaws in the methodology and interpretation of the results, raising doubts about the completeness and accuracy of the data.[30]

In 1980, the FDA appointed an independent investigative panel, the Public Board of Inquiry (PBOI), to re-examine the safety data on aspartame. The panel ultimately recommended that aspartame should not be approved for use in food until further studies, particularly on its potential carcinogenicity, were available.[31]

After further investigation and new studies by G.D. Searle & Company, the FDA revised its decision in 1981 and re-approved aspartame with an open-ended authorisation, but initially only for certain food categories such as dry products.[32] During this phase, the new FDA Commissioner Arthur Hull Hayes is said to have played a central role and actively lobbied for re-approval. This also led to controversy, as Hayes later took up a position at G.D. Searle & Company (the later NutraSweet Company).[33] The FDA approval of aspartame for carbonated beverages (1983), for confectionery, non-alcoholic beverages, low-alcohol beer (1993), and finally for all foods (1996) took place gradually[34] apparently without considering newer independent scientific studies.

Despite aspartame's eventual market re-approval, the sweetener remained highly controversial, and ever since, its safety has been repeatedly questioned. In the following decades, different organisations and authorities had a closer look at aspartame: the FDA in the USA, the Scientific Committee for Food (SCF) and European Food Safety Authority (EFSA) in the EU, and different World Health Organization (WHO) committees.

[30] https://www.sussex.ac.uk/webteam/gateway/file.php?name=doc-8---fda-bureau-of-drugs-searle-task-force-24march1976.pdf&site=25
[31] https://www.fda.gov/food/food-additives-petitions/timeline-selected-fda-activities-and-significant-events-addressing-aspartame
[32] https://archives.federalregister.gov/issue_slice/1981/7/24/38256-38289.pdf#page=30 p.38285-38308
[33] http://archive.gao.gov/d4t4/130780.pdf
[34] https://www.fda.gov/food/food-additives-petitions/timeline-selected-fda-activities-and-significant-events-addressing-aspartame

The more we learn about the EFSA decision approving aspartame, the more unanswered questions emerge.

Prof. Erik Millstone, Emeritus Professor in Science Policy Research Unit at the University of Sussex Business School, 2020.
www.newfoodmagazine.com/news/124838/aspartame/

3.2 ASPARTAME IN THE EU: A CONTROVERSIAL RE-APPROVAL

Aspartame was first approved in the EU in 1984 by the Scientific Committee for Food (SCF) for certain applications based on the assessment of safety studies provided by industry.[35] In the 1980s and 1990s, the authorisation was gradually extended, and in 1994 it was approved throughout the EU.[36] When EFSA was founded in 2002, it took over the responsibility for the evaluation of aspartame. EFSA was established in 2002 to ensure independent, transparent, and science-based risk assessment at the EU level.[37] Its creation was a response to various food scandals in the 1990s (such as the mad cow crisis) that shook public confidence in the food safety system.[38]

In 2009, a new regulation on the authorisation and evaluation of food additives came into force in the EU, Regulation (EC) No. 1333/2008 on food additives. This regulation standardised and updated the rules for the authorisation, use and safety assessment of food additives throughout the EU. The regulation required that all food additives that had been approved prior to their entry into force be subject to a re-evaluation of their safety by 2020. This was to ensure that the authorisations were based on the latest available scientific knowledge.[39, 40] Aspartame was one of the first additives to be re-evaluated ahead of schedule due to concerns and public debate about its safety.[41]

THE EFSA EVALUATION PROCESS

The EFSA evaluation is a multi-stage process that comprises various steps and a review of the available scientific data. First, starting in 2011, EFSA collected and analysed all available scientific studies and data on aspartame, including industry-funded and independent studies from the scientific literature. This opened the door for the submission of as many industry studies as possible. The EFSA re-evaluation included toxicological, epidemiological and experimental data on the safety of aspartame. In 2013,

[35] https://ec.europa.eu/food/fs/sc/scf/out155_en.pdf
[36] https://www.efsa.europa.eu/en/press/news/111124-0
[37] https://www.efsa.europa.eu/en/about/about-efsa
[38] https://www.bpb.de/kurz-knapp/lexika/das-europalexikon/176731/bse-krise/
[39] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R1333&qid=1731066964187
[40] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32010R0257
[41] https://www.efsa.europa.eu/en/press/news/ans110526

EFSA published a draft scientific opinion on aspartame[42] and launched a public consultation to obtain feedback from third parties. Later on, EFSA held a consultation event, during which stakeholders were able to present their views and scientific arguments on the EFSA draft report.[43] The Food and Drink Europe Association[44] and the International Sweeteners Cooperation[45] expressed their support for the draft report, but there were numerous points of criticism from independent scientists, consumer and non-profit organisations:

- The EFSA panel that wrote the draft report was criticised for including several experts with industry connections.[46]
- Studies that showed no risks were often considered reliable without scrutiny, while studies that indicated potential risks were dismissed as unreliable.[47]
- Several participants criticised the recommended Acceptable Daily Intake (ADI) for aspartame, arguing that it was based on outdated and flawed studies from the 1970s, all of which were funded by the industry.[48, 49, 50, 51]
- In a 96-line section of EFSA's draft report, 60 lines were taken almost identically from a paper by a food industry consultancy and EFSA's conclusion is exactly the same as this industry paper.[52]
- The Center for Science in the Public Interest (CSPI) criticised that the independent Ramazzini studies were discredited and reiterated the reliability of these studies (see below Table 1 on page 28).[53]
- Important independent studies on other potential health risks of aspartame were not covered in the report.[54]

After the stakeholder event, two additional EFSA panel members were appointed, and the report was revised and finally published in December 2013. This report recommended a high ADI of 40 mg/kg body weight.[55] But two key issues remained after this revision, which raised questions about this supposed safe dose: on the one hand, some of the EFSA panel members were found to have industry connections; and on the other hand, the selection criteria for evaluating the reliability of the studies included in the assessment were put in question.

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[42] https://www.efsa.europa.eu/sites/default/files/consultation/130108.pdf
[43] https://www.efsa.europa.eu/en/topics/topic/aspartame
[44] https://www.efsa.europa.eu/sites/default/files/event/documentset/130409-p10.pdf
[45] https://www.efsa.europa.eu/sites/default/files/event/documentset/130409-p09.pdf
[46] https://www.efsa.europa.eu/sites/default/files/event/documentset/130409-p08.pdf
[47] https://www.efsa.europa.eu/sites/default/files/event/documentset/130409-p04.pdf
[48] https://www.efsa.europa.eu/sites/default/files/event/documentset/130409-p08.pdf
[49] https://www.efsa.europa.eu/sites/default/files/event/documentset/130409-p07.pdf
[50] https://www.efsa.europa.eu/sites/default/files/event/documentset/130409-p05.pdf
[51] https://www.efsa.europa.eu/sites/default/files/event/documentset/130409-p11.pdf
[52] https://www.efsa.europa.eu/sites/default/files/event/documentset/130409-p08.pdf
[53] https://www.efsa.europa.eu/sites/default/files/event/documentset/130409-p06.pdf
[54] https://www.efsa.europa.eu/sites/default/files/event/documentset/130409-p08.pdf

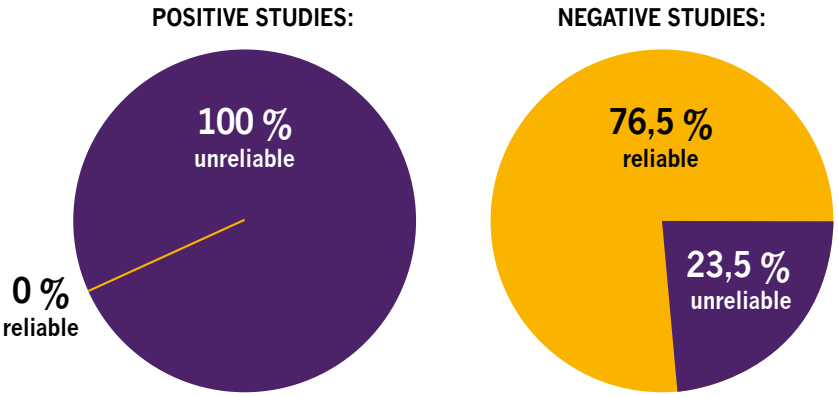
A SKEWED SELECTION OF STUDIES

A 2019 study warns that EFSA's toxicity assessment of aspartame had significant loopholes. Researchers Millstone and Dawson analysed the EFSA report from 2013.[56] Their most important findings were:

- **Asymmetric evaluation:** All of the 73 positive studies that indicated possible risks were classified as unreliable. On the contrary, 62 of the 81 studies with negative findings were considered reliable.[57, 58] This unequal treatment was criticised as biased, as the negative studies often showed methodological weaknesses.[59]

- **Strict criteria for positive studies:** Studies that indicated health concerns had to meet strict criteria, e.g. statistical significance and consistency, while negative studies were often accepted even if they had methodological flaws, such as small experimental group sizes and confounding factors like poor animal health.[60]

- **Lack of transparency:** EFSA often failed to make decisive criteria, assumptions, and selection reasons for the evaluation of the studies transparent, which violates internal guidelines from EFSA's Scientific Committee.[61]



EFSA's asymetric evaluation of aspartame studies. Positive studies indicate possible risks, negative studies do not.

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[55] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3496
[56] Millstone EP, Dawson E (2019) EFSA's toxicological assessment of aspartame: was it even-handedly trying to identify possible unreliable positives and unreliable negatives? Arch Public Health. 77:34. doi: 10.1186/s13690-019-0355-z
[57] Appendix 1 of Millstone paper (2019): https://static-content.springer.com/esm/art%3A10.1186%2Fs13690-019-0355-z/MediaObjects/13690_2019_355_MOESM1_ESM.pdf
[58] Millstone EP, Dawson E (2019) EFSA's toxicological assessment of aspartame: was it even-handedly trying to identify possible unreliable positives and unreliable negatives? Arch Public Health. 77:34. doi: 10.1186/s13690-019-0355-z p. 10
[59] Millstone EP, Dawson E (2019) EFSA's toxicological assessment of aspartame: was it even-handedly trying to identify possible unreliable positives and unreliable negatives? Arch Public Health. 77:34. doi: 10.1186/s13690-019-0355-z p. 18
[60] Millstone EP, Dawson E (2019) EFSA's toxicological assessment of aspartame: was it even-handedly trying to identify possible unreliable positives and unreliable negatives? Arch Public Health. 77:34. doi: 10.1186/s13690-019-0355-z p. 14-16
[61] Millstone EP, Dawson E (2019) EFSA's toxicological assessment of aspartame: was it even-handedly trying to identify possible unreliable positives and unreliable negatives? Arch Public Health. 77:34. doi: 10.1186/s13690-019-0355-z p. 11-12

The paper is both important and timely. The global health advice is to reduce sugar intake, yet much of the food industry—especially soft drinks—maintains the sweetness by substituting artificial sweeteners. Millstone and Dawson help expose that strategy for what it is, a continued sweetening of the world's diet. The healthy strategy is surely to tackle the cultural reinforcement of sweetness and to encourage less sweet foods and drinks, full stop. Surely we now argue: reduce both sugar and artificial alternatives.

Prof. Tim Lang, Professor of Food Policy, City University of London, 2019. https://medicalxpress.com/news/2019-07-safety-world-popular-artificial-sweetener.html

The conclusion of the study by Millstone and Dawson was that the 2013 assessment did not ensure sufficient safety for the consumption of aspartame and that EFSA should reform its assessment practices. Millstone and Dawson called for an independent, transparent re-evaluation to ensure a more balanced and consumer protection-oriented assessment.[62]

In addition, foodwatch looked at the 62 studies considered reliable[63] on which EFSA based its findings. This analysis shows that 30 studies[64] were conducted directly by the industry, namely the aspartame manufacturers Ajinomoto and NutraSweet. 29 of these 30 studies are not available for public review. In general, industry studies are kept confidential, which is a major loophole in most risk assessments relying on them – beyond the EFSA assessments of food additives. Furthermore, another eight studies were funded by the company NutraSweet,[65, 66, 67, 68, 69, 70, 71, 72] four studies by the food industry lobby International Life Sciences Institute (ILSI),[73, 74, 75, 76] and one study each by the companies General Food[77] and G.D. Searle Company.[78] The Magnuson study[79] was carried out by the Burdock Group, a food industry consultancy. This shows that nearly three-quarters (45 out of 62 papers) of the studies relied on by EFSA in its assessments were commissioned by industry or the authors declared links with industry.

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[62] Millstone EP, Dawson E (2019) EFSA's toxicological assessment of aspartame: was it even-handedly trying to identify possible unreliable positives and unreliable negatives? Arch Public Health. 77:34. doi: 10.1186/s13690-019-0355-z

[63] Appendix 1 of Millstone paper (2019): https://static-content.springer.com/esm/art%3A10.1186%2Fs13690-019-0355-z/MediaObjects/13690_2019_355_MOESM1_ESM.pdf

[64] E1, E2, E3, E19, E20, E21, E23; E24, E25, E26, E40, E41, E43, E46, E60, E61, E66, E67, E84, E85, E86, E87, E89, E95, E97, E104, E105 and E110 from https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3496 p. 152-158

[65] Spiers PA, Sabounjian L, Reiner A, Myers DK, Wurtman J, et al. (1998) Aspartame: neuropsychologic and neurophysiologic evaluation of acute and chronic effects. Am J Clin Nutr. 68(3):531-7. doi: 10.1093/ajcn/68.3.531

[66] Schiffman SS, Buckley CE 3rd, Sampson HA, Massey EW, et al. (1987) Aspartame and susceptibility to headache. N Engl J Med. 317(19):1181-5. doi: 10.1056/NEJM198711053171903

[67] Geha R, Buckley CE, Greenberger P, Patterson R, et al. (1993) Aspartame is no more likely than placebo to cause urticaria/angioedema: results of a multicenter, randomized, double-blind, placebo-controlled, crossover study. J Allergy Clin Immunol. 92(4):513-20. doi: 10.1016/0091-6749(93)90075-q

[68] Lapierre KA, Greenblatt DJ, Goddard JE, Harmatz JS, et al. (1990) The neuropsychiatric effects of aspartame in normal volunteers. J Clin Pharmacol. 30(5):454-60. doi: 10.1002/j.1552-4604.1990.tb03485.x

[69] Holder MD (1989) Effects of perinatal exposure to aspartame on rat pups. Neurotoxicol Teratol. 11(1):1-6. doi: 10.1016/0892-0362(89)90078-0

[70] Shaywitz BA, Sullivan CM, Anderson GM, Gillespie SM, et al. (1994) Aspartame, behavior, and cognitive function in children with attention deficit disorder. Pediatrics 93(1):70-5.

71 Shaywitz BA, Anderson GM, Novotni EJ, Ebersole JS, et al. (1994) Aspartame has no effect on seizures or epileptiform discharges in epileptic children. Ann Neurol. 35(1):98-103. doi: 10.1002/ana.410350115

[72] Rowan AJ, Shaywitz BA, Tuchman L, French JA, et al. (1995) Aspartame and seizure susceptibility: results of a clinical study in reportedly sensitive individuals. Epilepsia 36(3):270-5. doi: 10.1111/j.1528-1157.1995.tb00995.x

[73] Wolraich ML, Lindgren SD, Stumbo PJ, Steginк LD, et al. (1994) Effects of diets high in sucrose or aspartame on the behavior and cognitive performance of children. N Engl J Med. 330(5):301-7. doi: 10.1056/NEJM199402033300501

[74] Ryan-Harshman M, Leiter LA and Anderson GH (1987) Phenylalanine and aspartame fail to alter feeding behavior, mood and arousal in men. 39(2):247-53. doi: 10.1016/0031-9384(87)90017-5

[75] Saravis S, Schachar R, Zlotkin S, Leiter LA, et al. (1990) Aspartame: effects on learning, behavior, and mood. Pediatrics 86(1):75-83. 4

[76] Szucs EF, Barrett KE and Metcalfe DD (1986) The effects of aspartame on mast cells and basophils. Food Chem Toxicol. 24(2):171-4. doi: 10.1016/0278-6915(86)90353-4

[77] Porikos KP, Van Italie TB (1983) Diet-induced changes in serum transaminase and triglyceride levels in healthy adult men. Role of sucrose and excess calories. Am J Med. 75(4):624-30. doi: 10.1016/0002-9343(83)90444-8

[78] Leon AS, Hunninghake DB, Bell C, Rassin DK, et al. (1989) Safety of long-term large doses of aspartame. Arch Intern Med. 149(10):2318-24.

[79] Magnuson BA, Burdock GA, Doull J, Kroes, RM, et al. (2007) Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. Crit Rev Toxicol. 37(8):629-727. doi: 10.1080/10408440701516184

WHY SHOULD INDUSTRY-FUNDED RESEARCH NOT BE TAKEN FOR GRANTED?

"Researchers who take food industry funding do not believe that it affects their study design or interpretation and are outraged at the suggestion. Research, however, shows strong correlations between funding and research outcome."

Marion Nestle, New York University nutrition professor.[80]

The influence of industry funding on scientific research is well-documented and raises serious concerns about bias. Studies financed by companies often produce results favourable to their sponsors, not because the science is inherently flawed but because the questions asked, the methodologies chosen, and the interpretation of the data are often aligned with the sponsor's interests. This phenomenon has been observed across various industries in meta-analyses and systematic reviews.[81, 82, 83]

It is extensively discussed in the outstanding Unsavory Truth: How Food Companies Skew the Science of What We Eat by Marion Nestle.[84]

[80] https://www.theguardian.com/lifeandstyle/2016/dec/12/studies-health-nutrition-sugar-coca-cola-marion-nestle

[81] https://www.cochrane.org/MR000033/METHOD_industry-sponsorship-and-research-outcome

[82] https://link.springer.com/article/10.1007/s00134-018-5293-7

[83] https://pmc.ncbi.nlm.nih.gov/articles/PMC6603460/ In 2015 Coca-Cola, in association with Mexico's National Council for Science and Technology, established a yearly $100 000 grant for Mexican scientists. This grant was named after Ruben Lisker, a widely admired clinical researcher who passed away in 2015. The grant review panel includes nine well-established and highly respected Mexican scientists. As Marion Nestle describes in depth in her new book, Unsavory Truth: How Food Companies Skew the Science of What We Eat, Coca-Cola appears to be applying well-known strategies from the industry "playbook" to influence health research. Unsavory Truth's important contribution is encouraging nutrition and public health professionals to recognize food industry influence and to transparently disclose financial relationships with companies. The book provides some recommendations (although difficult to implement) to manage the impact of industry funding on scientific integrity.

[84] Nestle M (2018) Unsavory Truth: How Food Companies Skew the Science of What We Eat. Basic Books

In response to Millstone and Dawson's investigation, two EFSA representatives published a letter claiming they identified only 37 positive studies on aspartame in the 2013 EFSA report, far fewer than the 73 cited by Millstone and Dawson. Of these, 21 studies were deemed reliable and likely considered in the EFSA assessment.[85] Millstone and Dawson questioned why the reliable studies showing adverse effects did not influence the outcome or lead to a reduction in the ADI.[86]

[85] Kass GEN, Lodi F (2020) Letter to the editor regarding the article 'EFSA's toxicological assessment of aspartame: was it even-handedly trying to identify possible unreliable positives and unreliable negatives?' Arch Public Health. 78:14. doi: 10.1186/s13690-020-0395-4

[86] Millstone EP, Dawson E (2020) Why did EFSA not reduce its ADI for aspartame or recommend its use should no longer be permitted? Arch Public Health. 78(1):112. doi: 10.1186/s13690-020-00489-w

INDUSTRY TIES: HOW EFSA'S INDEPENDENCE MAY HAVE BEEN COMPROMISED

Was an independent assessment with the EFSA Panel even possible for the draft and final report? According to a Corporate Europe Observatory (CEO) analysis, some experts had industry links. Six members (out of 17 for the draft report and 19 for the final report) and an assistant expert with industry connections were involved in EFSA's aspartame assessment.[87, 88] The panellists' and experts' links with industry seemed to be multiple: several consultants for producers of aspartame and low-calorie products, and for a supermarket chain, laboratory funding by a big food company, links to lobby organisations like Food Industries Association of Austria (FIAA), Fédération de l'Industrie Alimentaire (FEVIA), International Organization of Flavor Industries (IOFI) and US Flavor and Extract Manufacturers Association (FEMA),[89] and ILSI – a food industry lobby group.[90, 91, 92, 93]

The EFSA's approach to transparency during this period raised concerns. In 2009, a brief EFSA report on the evaluation of the Ramazzini studies (see table in Chapter 4) mentioned that a panel member abstained from the discussion due to potential conflicts of interest, and this individual was identified by name.[94] However, in the 2013 draft report on aspartame, it was only vaguely noted that a panel member refrained from the discussion due to potential conflicts of interest, without specifying who this was.[95] In the final 2013 report, even this vague and unclear reference was omitted, despite no changes to the panel's composition. This created the impression that the conflict of interest had vanished, yet no panel member was formally excluded.[96]

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87 https://www.corporateeurope.org/sites/default/files/publications/efsa_ans_panel.pdf
88 https://www.corporateeurope.org/en/efsa/2011/09/eu-food-additive-experts-fail-declare-links-food-industry
89 https://www.corporateeurope.org/sites/default/files/publications/efsa_ans_panel.pdf
90 https://www.corporateeurope.org/en/efsa/2011/09/eu-food-additive-experts-fail-declare-links-food-industry
91 https://taz.de/Lebensmittelsicherheit-in-der-EU/!5104642/
92 https://www.eurotox.com/wp-content/uploads/2024/10/2024-Merit-IR_web.pdf
93 https://www.bezpecnostpotravin.cz/UserFiles/File/Kvasnickova/ILSI_Packagingsym.pdf
94 https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2009.1015
95 https://www.efsa.europa.eu/sites/default/files/consultation/130108.pdf
96 https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3496

In my opinion, based on this research, the question of whether commercial conflicts of interest may have affected the panel's report can never be adequately ruled out because all meetings all took place behind closed doors.

Prof. Erik Millstone, Emeritus Professor in the Science Policy Research Unit at the University of Sussex Business School, 2019.
www.medicalnewstoday.com/articles/325848#Are-there-conflicts-of-interest-at-play

In addition, the 2013 Corporate Europe Observatory report "Unhappy Meal. The European Food Safety Authority's independence problem" analysed all links between EFSA experts and the food industry at the time. According to the report, almost 60% of all experts sitting on various EFSA panels had direct or indirect links to the industry. Furthermore, EFSA accepted it as unproblematic if less than 25% of an expert's research budget came from private sources. This calculation was made by the experts themselves and was accepted by the agency without close scrutiny.[97]

SUMMARY

The history of aspartame's approval and evaluations highlights how the industry constantly managed to get its interests prioritised in such assessments. EFSA played a key role in this dynamic, allowing the aspartame lobby significant influence by prioritising industry-funded research, appointing experts with industry ties to its panels, relying on outdated studies from manufacturers, and dismissing more recent independent research. These tactics have enabled the food industry to keep aspartame on the market, push low-calorie products, and block regulatory authorities from adopting a more consumer-oriented approach. The next section examines why concerns persist and what independent studies say about aspartame.

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[97] https://corporateeurope.org/sites/default/files/attachments/unhappy_meal_report_23_10_2013.pdf

4 WHAT INDEPENDENT STUDIES REVEAL

- Independent scientists and organisations, such as the International Agency for Research on Cancer (IARC), have raised concerns.
- The Ramazzini Institute, an independent research institute, conducted multiple rigorous long-term animal studies suggesting potential cancer risks linked to aspartame. Their research and findings were cross-checked by other scientists, confirming their validity. The industry tried to discredit the Ramazzini Institute by criticising its laboratory practices rather than addressing the scientific findings.
- Independent epidemiological studies also highlighted concerns, using robust models to evaluate the health risks associated with aspartame.
- IARC classified aspartame as possibly carcinogenic (category 2B), although a minority of its working group supported an even higher hazard classification (category 2A).
- Conclusion: As of today, the available scientific evidence on aspartame does not allow for the dismissal of cancer concerns, even if further understanding of the mechanisms of action of the substance and its effects is still needed.

Aspartame has been widely used as a sweetener for decades, yet concerns about its potential health risks continue to surface. Are these concerns backed by evidence, or can they be dismissed outright? To answer this, it is necessary to tackle a deeper question: How can it be determined if a substance poses a threat to human health? It is ethically unacceptable and, therefore, impossible for scientists to experiment on humans by exposing them to high doses and comparing their outcomes to a control group. Instead, scientists use three main approaches to assess chemical safety:

- **Toxicology studies** are mostly carried out in vivo, on animals, to observe and understand the health effects of substances on living organisms. The results of animal studies are then extrapolated to predict potential effects for humans. Methodologies to study these effects are increasingly also being developed in vitro (in test tubes, outside of living organisms) and in silico (via computational models), but they are currently not yet fully developed to comprehensively study complex health effects (such as carcinogenicity) as animal studies allow.

- **Mechanistic studies** examine the biological or chemical events responsible for or associated with observed effects. They provide information about the mechanisms (at cellular, physiological or molecular levels) through which a substance will have an effect.

- **Epidemiological studies** investigate the distribution of diseases within the population and the factors that determine this distribution. They analyse large groups of people to try to identify associations between, e.g. exposure to a certain substance, such as a sweetener, and the occurrence of a health condition such as cancer. These studies can show correlations, but they cannot definitively prove causality.

None of these methods alone can sufficiently be relied on to confidently conclude hazard and risk in the context of a regulatory assessment, which is why they are combined. This is especially necessary for the evaluation of complex health endpoints such as carcinogenicity.

4.1 EVIDENCE FROM TOXICOLOGICAL RESEARCH: A CLEAR WARNING

Long-term toxicology studies on animals aim to investigate the harmful health effects of a substance over time, such as the potential for carcinogenicity or other chronic harmful effects. They are often conducted on rodents, particularly rats and mice. These species are particularly suitable for such studies due to their biological characteristics, short life spans, and the availability of standardised models to study them. The dose and duration of exposure to a substance can be precisely controlled in these studies. Scientists can specifically test different concentrations and aim at establishing clear dose-response relationships (when possible).[98]

The Ramazzini Institute published a series of long-term toxicological studies on the effects of aspartame in rats and mice. The Italian research institute, founded in the 1970s by Dr Cesare Maltoni, specialises in the study of carcinogenic substances and environmental factors. Named after Bernardino

[98] https://www.oecd.org/en/publications/test-no-451-carcinogenicity-studies_9789264071186-en.html

Ramazzini, a pioneer in occupational medicine, the institute focuses on long-term animal studies to provide a scientific basis for cancer prevention.[99] It is an independent non-profit social cooperative funded by more than 35,000 members. The institute is highly regarded for its contributions to toxicology, particularly its research on formaldehyde, vinyl chloride, and asbestos, which provided significant evidence for the subsequent classification of these substances as carcinogenic, including at the level of the IARC.[100] Global regulatory initiatives, including the ban on asbestos, have benefited from the work of the Ramazzini Institute.[101]

Over the years, industry has kept criticising the methodologies used by the institute to carry out its work, for example, the prolonged observation of laboratory animals and the conditions under which they were kept. Despite this, the Ramazzini Institute is a major authority in cancer research and the prevention of health risks.[102] Its work demonstrates how independent research can strengthen public health protection.

The institute conducted long-term studies on aspartame, exposing rats and mice to various doses throughout their lifespans. Their findings revealed a dose-dependent increase in lymphomas, leukaemias, and other tumours, including cancers in the mammary glands and urinary tract. The studies suggested that aspartame could have carcinogenic effects even at levels close to human exposure that regulatory authorities consider safe. Table 1 shows the results of the numerous studies in detail.

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[99] https://www.istitutoramazzini.it/about/
[100] https://glyphosatestudy.org/de/about-us/
[101] https://collegiumramazzini.org/news/detail/130
[102] Gift JS, Caldwell JC, Jinot J, Evans MV, et al. (2013) Scientific Considerations for Evaluating Cancer Bioassays Conducted by the Ramazzini Institute. Environ Health Perspect. 121(11-12):1253-63. doi: 10.1289/ehp.1306661
[103] Soffritti M, Belpoggi F, Degli Esposti D, Lambertini L (2005) Aspartame induces lymphomas and leukaemias in rats. Eur. J. Oncol. 10 :107–116.
[104] Soffritti M, Belpoggi F, Degli Esposti D, Lambertini L, et al. (2006) First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. Environ Health Perspect. 114: 379-385. doi: 10.1289/ehp.8711
[105] Belpoggi F, Soffritti M, Padovani M, Degli Esposti D, et al. (2006) Results of long-term carcinogenicity bioassay on Sprague-Dawley rats exposed to aspartame administered in feed. Ann N Y Acad Sci. 1076:559-77. doi: 10.1196/annals.1371.080
[106] Soffritti M, Belpoggi F, Tibaldi E, Degli Esposti E, et al. (2007) Life-span exposure to low doses of aspartame beginning during prenatal life increases cancer effects in rats. Environ Health Perspect. 115(9):1293-7. doi: 10.1289/ehp.10271
[107] Soffritti M, Belpoggi F, Manservigi M, Tibaldi E, et al. (2010) Aspartame administered in feed, beginning prenatally through life span, induces cancers of the liver and lung in male Swiss mice. Am J Ind Med. 53:1197-206. doi: 10.1002/ajim.20896
[108] Gnudi F, Panzacchi S, Tibaldi E, Iuliani M, et al. (2023) Hemolymphoreticular Neoplasias from the Ramazzini Institute Long-term Mice and Rat Studies on Aspartame. Ann Glob Health. 89(1):43. doi: 10.5334/aogh.4163

PUBLICATION YEAR	ANIMAL MODEL	NUMBER OF DOSE GROUPS	DURATION	RESULTS
2005[103]	Sprague-Dawley (rats)	7	8th week up to 151 weeks	■ statistically significant increase in lymphomas and leukaemias (F) ■ no significant effect (M) ■ no increase in brain tumours (M, F)
2006a[104]	Sprague-Dawley (rats)	7	8th week up to 151 weeks	■ increased incidence of malignant-tumour–bearing animals (M, F) ■ statistically significant dose-dependent increase in lymphomas and leukaemias (M, F) ■ statistically significant increase in dysplastic lesions and carcinomas of the renal pelvis and ureter combined (F) ■ increased incidence of malignant schwannomas of the peripheral nerves (M)
2006b[105]	Sprague-Dawley (rats)	7	8th week up to 151 weeks	■ statistically significant increased incidence of transitional cell carcinomas of the renal pelvis and ureter (F) ■ increase in lymphomas and leukaemias, with a positive significant trend (M, F) ■ statistically significant increased incidence of transitional cell carcinomas
2007[106]	Sprague-Dawley (rats)	3	12th day of foetal life up to 144 weeks	■ significant dose-related increase of malignant tumour–bearing animals (M) ■ significant increase in incidence of lymphomas/leukaemias (M, F) ■ significant dose-related increase in incidence of mammary cancer (F) ■ slightly reduced survival rate compared to control group ■ prenatal exposure increases incidence of lymphomas/leukaemias compared to postnatal exposure (F) ■ acceleration of onset of tumours of the renal pelvis and ureter (F)
2010[107]	Swiss (mice)	5	12th day of foetal life up to 130 weeks	■ significant dose-related increased incidence of hepatocellular carcinoms and ■ alveolar/bronchiolar carcinoma (M) ■ no increase of tumour incidence (F)
2023[108]	Sprague-Dawley rats	Using data of 2006a paper		■ statistically significant increases in lymphomas (all types) and leukaemias (all types) (M, F)
	Sprague-Dawley rats	Using data of 2007 paper		■ statistically significant increases in lymphomas (all types) (F)
	Swiss mice	Using data of 20010 paper		■ statistically significant increase in leukaemias (all types) (M, F)

Table 1: The Ramazzini Studies

F – female, M – male

Over the years, the Ramazzini Institute's studies have attracted both attention and criticism:

- To date, a central point of criticism remains the long-term observation of the animals until their natural death, which goes beyond the standardised 24 months of the OECD Test Guidelines No. 451. Critics have complained that this could lead to an increase in age-related tumours, but the institute has always argued that longer observation is necessary to detect tumours that develop late in the life cycle.[109]

- According to the Collegium Ramazzini, the criticisms from the chemical manufacturing and processed food industries and regulatory agencies were harsh and unjustified. These critics alleged that the institute's animal facility was poorly managed and that the test animals were affected by uncontrolled infections. However, the Ramazzini Institute has emphasised that its conditions have always been controlled and comparable with those of other long-term studies.[110]

- Further criticism concerns the high spontaneous incidence of certain tumours in Sprague-Dawley rats and the deviating dose-response relationships that do not always meet expectations. The institute has responded that such effects can be explained by specific metabolic mechanisms.

- In addition, a lack of transparency in raw data and methodological deviations from OECD standards were cited, although the institute has emphasised that its methods are appropriate for the long-term assessment of carcinogenicity[111] and has shared extensive details with EFSA.[112]

Despite these criticisms, independent re-analyses have supported the Ramazzini Institute's findings and confirmed the scientific robustness and transparency of its methodologies.

- A 2020 re-analysis by Landrigan and Straif highlighted the value of the institute's long-term bioassays in identifying potential cancer risks and the methodologies chosen to investigate them. The study confirmed the validity of the findings, namely a significant increase in lymphomas and leukaemias in animals exposed to aspartame, with higher doses leading to higher disease rates. Notably, animals exposed to aspartame before birth developed cancer more frequently and at lower doses compared to those exposed as adults.[113]

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[109] https://cordis.europa.eu/article/id/25605-findings-on-risk-from-aspartame-are-inconclusive-says-efsa
[110] https://www.collegiumramazzini.org/news/detail/211
[111] Soffritti M, Padovani M, Tibaldi E, Falcioni L, et al. (2014) The carcinogenic effects of aspartame: The urgent need for regulatory re-evaluation. Am J Ind Med.57(4):383-97. doi: 10.1002/ajim.22296
[112] https://www.efsa.europa.eu/sites/default/files/event/documentset/corporate060505-ax1.pdf
[113] Landrigan PJ, Straif K (2021) Aspartame and cancer - new evidence for causation. Environ Health. 12;20(1):42. doi: 10.1186/s12940-021-00725-y

We call upon all national and international public health agencies to urgently reexamine their assessments of aspartame's risks to health – especially the risks of prenatal exposure – in light of these newly revalidated findings from the Ramazzini Institute. This call reiterates a plea for such reexamination that was made by Ramazzini Institute scientists in 2014. We call upon food agencies in countries around the world to reassess Acceptable Daily Intake (ADI) levels for aspartame.

Kurt Straif, Philip J. Landrigan in Landrigan PJ, Straif K (2021) Aspartame and cancer - new evidence for causation. Environ Health. 12;20(1):42. doi: 10.1186/s12940-021-00725-y

- The scientific validity and quality of the Ramazzini Institute's work was also confirmed by an analysis by a scientist from the US National Toxicology Program (NTP), who demonstrated the high level of agreement between the work of the Ramazzini Institute and the US NTP on numerous chemical substances.[114] This contradicted criticisms who had previously attacked the robustness and relevance of the methodologies used to study cancer occurrence.

- As previously mentioned, IARC, as a major authority in cancer research, used the results of the Ramazzini Institute in its classification of aspartame as "possibly carcinogenic to humans" (Group 2B). Despite discussions in relation to methodology, the indications of tumours were taken seriously.[115]

- Caldwell et al. addressed criticisms of the Ramazzini rat studies regarding high rates of respiratory infections in older animals. They refuted the claim that these infections caused the dose-dependent increase in lymphomas and leukaemias, showing that such tumours occurred in only a few animals, making an infection-tumour link unlikely.[116] Overall, the researchers underlined the importance of the Ramazzini Institute's work for the debate on the safety of aspartame.

Taken together, the studies of the Ramazzini Institute have provided important findings on the potential carcinogenicity of aspartame despite various methodological criticisms against the institute. Independent re-analyses have supported many of the results, in particular, the link between aspartame exposure and increased rates of lymphomas, leukaemias, and other types of tumours. The institute's protocols have been detailed in a transparent way.

No experimental study is flawless or capable of addressing every scientific question in a single effort. However, the re-analyses of the Ramazzini studies, combined with their inclusion in the IARC discussions, underscore their scientific significance. While further research may be needed to resolve remaining uncertainties, dismissing these findings as irrelevant would be unjustified.

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114 Huff J (2002) 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 N Y Acad Sci. 982:208-30. doi: 10.1111/j.1749-6632.2002.tb04935.x

115 https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Aspartame-Methyleugenol-And-Isoeugenol-2024

116 Millstone EP, Dawson E (2019) EFSA's toxicological assessment of aspartame: was it even-handedly trying to identify possible unreliable positives and unreliable negatives? Arch Public Health. 77:34. doi: 10.1186/s13690-019-0355-z p. 7

4.2 HUMAN DATA: WHAT EPIDEMIOLOGY REVEALS ABOUT ASPARTAME

Epidemiological studies complement animal research by offering valuable insights into real-world exposure conditions and their potential associations with health conditions. In the case of aspartame, the available studies with a large number of participants explore potential associations between its consumption and several conditions, including cancer, in humans, adjusting for individual factors such as diet, lifestyle, and genetic predisposition.

Two prospective epidemiologic studies – the INSERM study (2022) and the Schernhammer study (2012) – are particularly key. Both analysed large population groups over long periods of time and investigated the associations between aspartame consumption and cancer risk. Their results complemented the findings from animal experiments and raised important questions about the safety of aspartame, while also highlighting the strengths and challenges of epidemiological research.

The 2012 Schernhammer study examined the long-term associations between the consumption of diet and regular sodas and the risk of cancer, based on data from over 77,000 women and 47,000 men from two large US cohorts over 22 years. Men who consumed more than one diet soda per day had a significantly increased risk of non-Hodgkin's lymphoma (31%) and multiple myeloma (102%). No such association was found in women. Combined data from men and women showed an increased risk of blood cancer when consuming diet sodas (42%). Interestingly, consumption of regular sugary sodas also showed an increased risk of non-Hodgkin's lymphoma in men (66%), complicating the interpretation. The study underlined the need for further research into gender-specific differences in aspartame metabolism.[117]

An INSERM study from 2022 examined over 102,000 French adults as part of the NutriNet-Santé cohort.[118] This large cohort is part of an ongoing French investigation launched in 2009 to examine associations between

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[117] Schernhammer ES, Bertrand KA, Birmann BM, Sampson L, et al. (2012) Consumption of artificial sweetener- and sugar-containing soda and risk of lymphoma and leukemia in men and women. Am J Clin Nutr. 96(6):1419-28. doi: 10.3945/ajcn.111.030833

[118] https://etude-nutrinet-sante.fr/

diet, lifestyle, and health outcomes. Participants provide detailed dietary and health information over time, enabling researchers to study the impact of nutrition on chronic diseases like cancer and obesity.

As part of this investigation, INSERM researchers analysed the association between the consumption of artificial sweeteners – including aspartame, acesulfame-K and sucralose – and the risk of cancer.[119] Over a median period of 7.8 years, researchers already found increased cancer risk at rather low levels of consumption between half a soda can and one can a day. Aspartame was particularly associated with an increased risk of breast cancer (+22 %) and obesity-associated cancers (+15 %).

The study collected detailed information about what people eat and adjusted for factors that could affect the results, like age, gender, body weight, smoking, and existing health conditions, to make the findings as reliable as possible. Additional verifications showed the results were strong, but the researchers acknowledged there might still be some bias and that more research is needed.[120]

While epidemiological studies such as these have weaknesses – such as potential inaccuracies in self-reported dietary data and the challenge of establishing causality – both studies took steps to minimise these. Long-term observations, large sample sizes, and accounting for numerous confounding factors such as age, diet, and lifestyle increased the reliability of the results. Nevertheless, some questions remain, and further research is needed to clarify the exact biological mechanisms behind the observations.

4.3 IARC SPEAKS: ASPARTAME COULD BE A CARCINOGEN

The findings of some of those studies provide important content for IARC assessment. IARC is the world's leading body for the scientific investigation of carcinogenic substances set up by the United Nations World Health Organization (WHO). IARC working groups independently and comprehensively review all publicly available scientific studies and reports at the time of evaluation.

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[119] Debras C, Chazelas E, Srour B, Druesne-Pecollo N, et al. (2022) Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study. PLoS Med. 19(3):e1003950. doi: 10.1371/journal.pmed.1003950

[120] Debras C, Chazelas E, Srour B, Druesne-Pecollo N, et al. (2022) Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study. PLoS Med. 19(3):e1003950. doi: 10.1371/journal.pmed.1003950

IARC prioritises independence and transparency in its evaluation process. The WHO defines the roles of working group members, invited experts, observers, and health organisation representatives. Working group members who lead the scientific investigation and classification must be free from conflicts of interest. All participants submit detailed declarations, and individuals with current industry ties, such as financial support or consultancy roles, are excluded. IARC publishes the names and professional backgrounds of the experts, selected based on their research expertise and publication history. This rigorous process safeguards the integrity and independence of IARC's assessments.

In addition, IARC has strict guidelines for observers and invited experts to ensure the independence of its assessments. Observers are not allowed to participate in the preparation or the assessments and must avoid any contact with members before or during the meeting.[121] Conflicts of interest are disclosed, and members are encouraged to report any attempts to influence them. In the aspartame assessment, five out of eight observers declared conflicts of interest. Invited experts are not allowed to make decisions or draft texts; their role is limited to advice and is strictly monitored. The only invited expert for the aspartame investigation disclosed links to the manufacturer Ajinomoto. Through transparency and clear limitations, IARC ensures that potential conflicts of interest do not compromise the independence of its assessments.[122]

As a result of Working Group evaluations, detailed monographs are published, and all investigated substances are classified into one of the following four categories:[123]

1. **Carcinogenic to humans**
2. **2A Probably carcinogenic to humans**
3. **2B Possibly carcinogenic to humans**
4. **3 Not classifiable as to its carcinogenicity to humans**

IARC first investigated aspartame in 2023 and classified it as category 2B ("possibly carcinogenic to humans") based on a comprehensive assessment of all publicly available scientific data on aspartame. This classification was the result of a review of existing epidemiological, toxicological, and mechanistic studies by an IARC working group.[124] A minority of this group favoured a

[121] https://monographs.iarc.who.int/guidelines-for-observers-at-iarc-monographs-meetings/
[122] https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Aspartame-Methyleugenol-And-Isoeugenol-2024 p. 3-7 footnotes
[123] https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf
[124] https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Aspartame-Methyleugenol-And-Isoeugenol-2024

stricter classification.[125] The full monograph was published in April 2024.[126] Toxicological studies conducted on various animal species revealed an increased occurrence of malignant tumours, as well as combinations of benign and malignant tumours, in mice and rats. While the IARC working group acknowledged criticisms of the methodologies used in these studies, it still identified limited evidence of carcinogenicity. A minority within the working group, however, expressed no concerns about the methodologies and believed these studies provided stronger evidence of the substance's potential to cause cancer.[127]

IARC also evaluated studies examining potential links between aspartame consumption and cancer in humans. Epidemiological studies identified indications of an association between aspartame consumption and an increased risk of certain cancers. IARC concluded that there is credible evidence suggesting a positive link between aspartame consumption and liver cancer in humans. However, the epidemiological evidence available was not deemed sufficient to draw definitive conclusions about the relationship between aspartame consumption and the risk of other types of cancer or cancer risk overall.

IARC evaluated mechanistic studies on aspartame and found evidence suggesting that aspartame induces oxidative stress and potentially chronic inflammation in experimental systems. However, the overall evidence regarding the extent to which the substance meets the key characteristics of carcinogens was deemed limited and inconsistent.[128]

Based on the limited evidence from epidemiological, animal experimental, and mechanistic studies, IARC decided to classify aspartame as category 2B ("possibly carcinogenic to humans"). This classification means that the potential for cancer causation cannot be ruled out based on all the available evidence reviewed.

A minority of the working group favoured a stricter category 2A classification based on sufficient evidence for cancer in experimental animals and limited evidence from epidemiological and mechanistic studies. The full IARC monograph states that further research is needed to better understand the causality and extent of the carcinogenicity potential.[128, 130]

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[125] https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Aspartame-Methyleugenol-And-Isoeugenol-2024 p. 489
[126] https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Aspartame-Methyleugenol-And-Isoeugenol-2024
[127] https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Aspartame-Methyleugenol-And-Isoeugenol-2024 p. 483-484, 488
[128] https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Aspartame-Methyleugenol-And-Isoeugenol-2024 p. 494
[129] https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Aspartame-Methyleugenol-And-Isoeugenol-2024 p.489
[130] https://www.who.int/news/item/14-07-2023-aspartame-hazard-and-risk-assessment-results-released

The door is still open that aspartame could be carcinogenic. That door could not be completely closed after the assessment.

Prof. Eva Schernhammer, Adjunct Professor of epidemiology at Harvard's TH Chan School of Public Health and a member of the IARC evaluation on aspartame, 2024.
www.theguardian.com/us-news/article/2024/jun/12/aspartame-health-effects-risks

4.4 OTHER POTENTIAL HEALTH RISKS

Beyond the potential cancer risk, scientific investigations have also pointed to potential associations between aspartame consumption and other health effects. This section highlights a non-exhaustive list of independent studies, which contribute to the growing evidence pointing to concerns related to effects on the cardiovascular system, the microbiome, and the central nervous system. These studies are preliminary estimations of additional health risks. Although not conclusive, they indicate the need for further research and caution.

Cardiovascular diseases: A 2022 epidemiological study based on the French NutriNet-Santé cohort analysed data from over 100,000 participants. It found a statistically significant higher risk (+17%) of cerebrovascular events, such as strokes, among aspartame consumers compared to non-consumers. However, no significant association was observed with other cardiovascular diseases like heart attacks or coronary heart disease. These findings suggest aspartame may pose a specific risk for cerebrovascular events, that is, conditions that affect the blood flow to the brain and point to the need for further research.[131]

Type 2 diabetes (T2D): Another NutriNet-Santé-based study from 2023 analysed the link between aspartame consumption and T2D risk. High aspartame intake was associated with a higher risk of developing T2D (+63%) compared to non-consumers. The results remained significant after accounting for factors such as diet, weight changes, and lifestyle. These findings suggest that aspartame, commonly used as a sugar substitute, may contribute to T2D risk rather than prevent it. Further research is needed to confirm causality and mechanisms.[132]

Effects on microbiome composition: The Suez et al. (2014, 2022) studies found that sweeteners can impact glucose metabolism via gut microbiota changes. The 2022 study specifically examined saccharin, sucralose, aspartame, and stevia. While saccharin and sucralose impaired glucose tolerance, aspartame had no significant glycaemic effects in healthy adults. However, aspartame altered gut microbiome composition, showing that it is not enti-

[131] Debras C, Chazelas E, Sellem L, Porcher R, et al. (2022) Artificial sweeteners and risk of cardiovascular diseases: results from the prospective NutriNet-Santé cohort. BMJ. 378:e071204. doi: 10.1136/bmj-2022-071204
[132] Debras C, Deschasaux-Tanguy M, Chazelas E, Sellem L, et al. (2023) Artificial Sweeteners and Risk of Type 2 Diabetes in the Prospective NutriNet-Santé Cohort. Diabetes Care. 46(9):1681-1690. doi: 10.2337/dc23-0206

rely inert. These findings suggest potential microbiome-mediated impacts of aspartame.[133, 134]

Emerging neurotoxicity concerns: A recent study published in Nature found that consuming aspartame at smaller doses (7,5 mg/ kg body weight) than those currently recommended by the US regulatory FDA (50 mg/kg body weight) caused learning and memory issues in male mice within four weeks of consumption already. These effects were passed on to offspring of the first generation (both male and female) through the father.[135] The study findings suggest that the adverse behavioural effects of aspartame among consumers and their descendants may need further investigation.

Another recent study found that aspartame disrupts memory capacity, sleeping cycles, and brain functioning. The substance appears to alter brain chemistry by disrupting the metabolism of the neurotransmitters in the hippocampus, the part of the brain that controls memory. While warranting further investigations, these findings raise concerns about aspartame's potential impact on brain health and its effects on future generations.[136]

Emerging scientific evidence suggests that aspartame may pose multiple health risks, including cardiovascular, metabolic, microbiome, and neurocognitive health. It suggests that further research is needed to fully understand the potential long-term effects of the substance on health.

SUMMARY

Independent research has shown that aspartame cannot be safely used in food and drinks, with toxicological and epidemiological studies demonstrating in a complementary way that aspartame consumption is associated with a higher risk of cancer. While further scientific questions (e.g. on the mechanisms of action of the substance and its effects) still need to be investigated, the available scientific evidence is robust enough to warrant a precautionary approach to the safety of aspartame.

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[133] Suez J, Korem T, Zeevi D, Zilberman-Schapira G, et al. (2014) Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 514(7521):181-6. doi: 10.1038/nature13793

[134] Suez J, Cohen Y, Valdés-Mas R, Mor U, et al. (2022) Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance Cell 185(18):3307-3328. doi: 10.1016/j.cell.2022.07.016

[135] Jones SK, McCarthy DM, Stanwood GD, Schatschneider C, et al. (2023) Learning and memory deficits produced by aspartame are heritable via the paternal lineage. Sci Rep. 13(1):14326. doi: 10.1038/s41598-023-41213-2

[136] Bai H, Zuo X, Zhao C, Zhang S, et al. (2024) Non-nutritive Sweetener Aspartame Disrupts Circadian Behavior and Causes Memory Impairment in Mice. J Agric Food Chem. 72(42):23478-23492. doi: 10.1021/acs.jafc.4c05394

5 HOW JECFA PUT OUT A BIASED RISK ASSESSMENT

- The aspartame risk assessment of the Joint FAO-WHO Expert Committee on Food Additives (JECFA) is problematic because of the unclear criteria they apply to select the studies they rely on and the way they weigh the studies (industry vs independent) against another.

- Several JECFA panellists and supporting experts have previous or current links to industry groups, which raises questions about potential influence on JECFA's conclusions about aspartame. Meanwhile, some industry-funded lobby groups have influenced public opinion on food-related topics for decades.

The WHO International Agency for Research on Cancer (IARC) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) are two separate organisations affiliated with United Nations agencies. IARC operates under the World Health Organization (WHO), while JECFA is jointly managed by the Food and Agriculture Organization (FAO) and WHO. Their roles differ, leading them to evaluate substances at different levels and using distinct methodologies.

The cancer research institute IARC investigates the hazardous properties of substances as part of its monographs program – including but not limited to chemicals used as food additives. It investigates whether a substance is able to cause cancer under certain circumstances, and it proposes related scientific classifications for them.[137] IARC bases its assessments on all existing relevant scientific evidence. As demonstrated in the previous chapter, this approach was evident in the case of aspartame, where it was classified as "possibly carcinogenic".

JECFA, by contrast, is a risk evaluation body, that assesses the safety of substances and looks at the likelihood that the exposure to a substance materialises in harmful health effects (risk = hazard x exposure). Based on the findings of its evaluation, JECFA sets what is referred to as an Acceptable Daily Intake (ADI), which is the dose under which the substance is supposed to be unlikely to pose a health risk.

[137] https://monographs.iarc.who.int/home/iarc-monographs-general-information/

Neither IARC nor JECFA conduct regulatory assessments. Rather, they make their research results available to governments and institutions so that they can use them to take regulatory measures to protect health.

In 2023, IARC assessed the potential cancer hazard of aspartame for the first time and classified it as possibly carcinogenic (category 2B).[138] Two weeks later, JECFA began a new risk assessment at its 96th meeting. For ten days, 13 members and 13 supporting experts worked on a risk evaluation and as a result, they proposed an update of the so-called safe level of exposure through the setting up of an ADI for aspartame. All members and experts declared in advance that they had no conflicts of interest. The JECFA report covered both positive studies reporting an association between aspartame and cancer and negative studies reporting no association between aspartame and cancer. However, the conclusions of JECFA's final report excluded all positive studies and therefore found no concern for the consumption of aspartame. The new recommended ADI[139] remains unchanged compared to previous reports published in 1981 and 2016.[140]

5.1 JECFA DISMISSED CRITICAL RESEARCH

The 2023 JECFA analysis encompassed a variety of studies, including positive studies that showed a link between aspartame and cancer. The latter were exclusively long-term toxicological studies and epidemiological studies carried out by independent scientists. It is, however, striking that not even one such positive study was deemed to meet the JECFA selection requirements, and therefore, none of them were used to support the final conclusions of their risk assessment. From an outside point of view, it is not possible to understand the criteria used for selecting studies presented in the JECFA report.

In contrast, negative studies that showed no link between aspartame and cancer were viewed far less critically and seemingly less stringent standards were applied. Criteria that would lead to exclusion were not fully and transparently stated. All negative studies were approved by JECFA for the risk assessment of aspartame, even if there were concerns about the design or conduct by the JECFA panel.[141]

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[138] https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Aspartame-Methyleugenol-And-Isoeugenol-2024
[139] https://iris.who.int/bitstream/handle/10665/376279/9789240083059-eng.pdf?sequence=1
[140] https://apps.who.int/food-additives-contaminants-jecfa-database/Home/Chemical/62
[141] https://iris.who.int/bitstream/handle/10665/376279/9789240083059-eng.pdf?sequence=1

INDEPENDENT TOXICOLOGICAL RESEARCH: SET ASIDE

In the JECFA report, this was particularly noticeable in the conclusions regarding the results available from long-term toxicological animal studies. JECFA discussed the positive Ramazzini studies from 2005 to 2010 in detail in its report and cited numerous reasons for rejection, so that all results were ultimately not even considered in the conclusions of the risk assessment. The institute's working methods were also discredited in the report, i.e. not fulfilling the 24-month requirement for animal life span of OECD Test Guideline No. 451.[142] From a methodological point of view, the work conducted by the Ramazzini Institute stands out because the rats were not killed prematurely, and they were only examined after their death. It makes sense when investigating the occurrence of a disease such as cancer, which can sometimes manifest years or decades after the actual exposure to a cancer-causing agent and would not be possible to observe in a short-term study. This is relevant for humans and animals alike.

What JECFA fails to mention is that independent third-party reviews of the working methods and results of the institute validated its work – as shown in Chapter 4. Therefore, it is hard to understand why JECFA has continued to dismiss the findings of these studies in its risk assessment. If these findings had been fully considered, the ADI they established would likely have been significantly lower.

It is also striking that JECFA applied far less stringent standards when reviewing all negative long-term toxicological animal studies that show no link between aspartame and cancer. Uncertainties in the design or execution of three studies from the 1970s by the Searle company[143, 144, 145] and the Ajinomoto study from 1981,[146] were downplayed. These studies did not fulfil the OECD Test Guideline No. 451, a criticism that JECFA had raised when assessing the Ramazzini studies to justify dismissing their findings. And yet, this methodological aspect did not lead JECFA to dismiss the industry studies. This is equivalent to applying double standards in assessing studies. If the Ramazzini findings had been dismissed, then these industry studies should have been too.

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[142] https://www.oecd.org/en/publications/test-no-451-carcinogenicity-studies_9789264071186-en.html
[143] Anonymous. (1974) 18862: 104-week toxicity study in the mouse: final report to Hazleton Laboratories, Inc, Vienna (VA). Unpublished report by Searle Laboratories, GD Searle and Company, Chicago (IL).
[144] Anonymous. (1973) Two-year toxicity study in the rat: final report to Searle Laboratories, GD Searle and Company, Chicago, IL. Unpublished report by Hazleton Laboratories, Inc., Vienna, VA.
[145] Anonymous. (1974) Lifetime toxicity study in the rat: final report to Hazleton Laboratories, Inc, Vienna (VA). Unpublished report by Searle Laboratories, GD Searle and Company, Chicago (IL).
[146] Ishii H, Koshimizu T, Usami S, Fujimoto T (1981) Toxicity of aspartame and its diketopiperazine for Wistar rats by dietary administration for 104 weeks. Toxicology. 21(2):91–4. doi:10.1016/0300-483x(81)90119-0

In the remaining studies showing no effects, uncertainties were not addressed at all, even though all studies had much shorter lifetimes of rats and mice than the positive studies, namely 6-9 months.[147] The OECD Test Guideline No. 451 requires 24 months for rodents.[148]

This means that JECFA considered studies with animal lifetimes that are not in line with the requirements of standard test protocols for the study of long-term carcinogenicity in rodents as reliable. Therefore, these studies should have been excluded.

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[147] https://iris.who.int/bitstream/handle/10665/376279/9789240083059-eng.pdf?sequence=1 p. 6-9
[148] https://www.oecd.org/en/publications/test-no-451-carcinogenicity-studies_9789264071186-en.html

IMPORTANT EPIDEMIOLOGICAL STUDIES: DISREGARDED

The JECFA review of epidemiological cohort studies was not handled in a strictly scientific and transparent way. Again, all positive studies showing associations between aspartame and cancer were dismissed, while the negative studies showing no associations have, on the contrary, been given more weight in the assessment:

- Two US-data-based studies had negative results and showed no association between aspartame and cancer. No concerns about their design or results were raised by JECFA.
- Two US-data-based studies had positive results and showed an association between aspartame and cancer. Many concerns about their designs or results were raised by JECFA.[149]
- Six European-data-based studies showing associations between various types of cancer/mortality and aspartame consumption were discussed in detail. JECFA raised concerns over flaws in the design and results of studies and dismissed them in its assessment.[150]

The treatment of epidemiological studies showing positive associations with cancer risk is puzzling, especially considering the extensive efforts and transparency demonstrated by researchers to address the inherent uncertainties of such studies. A notable example is the recent NutriNet cohort study, conducted by the French National Institute of Public Health (INSERM).[151] This study revealed a significant increase in cancer incidence among individuals consuming rather low doses of aspartame – approximately 200 times lower than the current Acceptable Daily Intake (ADI) recommended by EFSA and JECFA.

According to EFSA and JECFA, an adult weighing 70 kg would need to consume more than 14 cans of a diet soft drink (containing 200 mg of aspartame per can) daily to exceed the ADI.[152] However, the findings from the French study suggest that consuming between half a can and one can per day could already increase cancer risk.[153]

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[149] https://iris.who.int/bitstream/handle/10665/376279/9789240083059-eng.pdf?sequence=1 p.12
[150] https://iris.who.int/bitstream/handle/10665/376279/9789240083059-eng.pdf?sequence=1 p. 12-13
[151] Debras C, Chazelas E, Srour B, Druesne-Pecollo N, et al. (2022) Artificial sweeteners and cancer risk: results from the NutriNet-Santé population-based cohort study. PLOS Med. 19(3):e1003950. doi: 10.1371/journal.pmed.1003950
[152] https://www.who.int/news/item/14-07-2023-aspartame-hazard-and-risk-assessment-results-released
[153] https://environnementsantepolitique.fr/2023/07/14/laspartame-edulcorant-utilise-couramment-depuis-une-quarantaine-dannees-dans-des-milliers-de-produits-de-consommation-quotidienne-dans-le-monde-entier-a-ete-declare/

The International Agency for Research on Cancer (IARC) regarded the NutriNet cohort study as "the most detailed" epidemiological study on aspartame exposure, noting its high-quality exposure assessment.[154] In comparison to most available studies, the NutriNet cohort study stood out due to its robust methodology. Additionally, 11 out of the 12 sensitivity analyses performed demonstrated that the results remained significant for all cancers, as well as for breast and obesity-related cancers.
This robustness was evident even when certain variables – such as smoking status or diabetes – were excluded from the analysis, further strengthening the reliability and credibility of the study's findings.

Only one model in the sensitivity analysis showed no significance. Instead of emphasising this fact, which reinforced the quality of the results from the NutriNet cohort study, JECFA presented it as a weakness. Due to the lack of significance in just one out of twelve models, the findings of the study were excluded from the conclusions of the risk assessment.

Furthermore, while IARC considered the positive findings from the study by Schernhammer et al., JECFA dismissed the relevance of its results in its final risk assessment.155 These findings, detailed in Chapter 4, were criticised due to differences in cancer incidence between sexes – a point of criticism that was not accompanied by any methodological concerns about the study.156 Yet, this single critique led to the dismissal of the study's positive findings. On the contrary, the results of negative studies appeared to have been accepted by the JECFA without such a critical consideration.

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[154] https://publications.iarc.who.int/627 p. 337
[155] Schernhammer ES, Bertrand KA, Birmann BM, Sampson L, et al. (2012) Consumption of artificial sweetener- and sugar-containing soda and risk of lymphoma and leukemia in men and women. Am J Clin Nutr. 96(6):1419-28. doi: 10.3945/ajcn.111.030833
[156] https://iris.who.int/bitstream/handle/10665/377542/9789240092549-eng.pdf?sequence=1

The problematic exposure doses that we were able to measure in NutriNet-Santé are much lower than the JECFA recommendation, between half a can and one can a day. This was also the case in the three studies that identified the link between aspartame and liver cancer.

Mathilde Touvier, INSERM CRESS/ EREN research director, NutriNetSanté cohort coordinator, 2023. https://environnementsantepolitique.fr/2023/07/14/laspartame-edulcorant-utilise-couramment-depuis-une-quarantaine-dannees-dans-des-milliers-de-produits-de-consommation-quotidienne-dans-le-monde-entier-a-ete-declare/, translated with Deepl.

THE ACCEPTABLE DAILY INTAKE – BASED ON A 1981 INDUSTRY STUDY

The new Acceptable Daily Intake (ADI) for aspartame remains unchanged from the previously established level of 40 mg/kg of body weight. This value is derived from the assessment of long-term toxicological animal studies. The study by Ishii et al. serves as the primary foundation for determining a safe level of exposure. However, this study is not only very old (1981) but was also published by the world's largest aspartame manufacturer, Ajinomoto.[157] It does not comply with international standard test guidelines, such as the OECD No. 451. As a reminder and by contrast, non-compliance with OECD Test Guidelines led JECFA to dismiss the findings of the studies carried out by the independent Ramazzini Institute.

Furthermore, the JECFA report emphasised[158] that the 1981 results were confirmed by a third-party review in 2019.[159] Two of the authors were reportedly employed by Ajinomoto, the world's largest aspartame manufacturer at the time. Another author worked for a company specialising in toxicologic pathology services, while the remaining two authors were associated with a consulting firm serving the food industry. In other words, none of the authors appeared to be entirely independent of industry ties.

However, an independent review necessitates the involvement of impartial scientists and institutions, free from any commercial interests in the study's outcomes. It cannot be conducted by the industry with direct financial stakes or its affiliated service providers. In this instance, it appears that the manufacturer effectively reviewed its own study, which JECFA subsequently presented as a third-party re-evaluation.

5.2 INDUSTRY TIES IN THE JECFA PANEL

This unequal treatment of industry-sponsored and independently funded studies raises fundamental questions about the independence and objectivity of JECFA. Links to the food industry may have played a role in favouring industry-friendly studies. The name of one organisation in particular keeps popping up, as it did in the 2013 EFSA assessment: the influential lobby group International Life Sciences Institute (ILSI).

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[157] Ishii H, Koshimizu T, Usami S, Fujimoto T (1981) Toxicity of aspartame and its diketopiperazine for Wistar rats by dietary administration for 104 weeks. Toxicology. 21(2):91–4. doi:10.1016/0300-483x(81)90119-0

[158] https://iris.who.int/bitstream/handle/10665/376279/9789240083059-eng.pdf?sequence=1 p. 7

[159] Shibui Y, Fujitani S, Iwata S, Lynch B, et al. (2019) Histological analyses of the Ishii (1981) rat carcinogenicity study of aspartame and comparison with the Ramazzini Institute studies. Regul Toxicol Pharmacol. 102:23–9. doi:10.1016/j.yrtph.2018.12.010

FOOD INDUSTRY LOBBY GROUP – INTERNATIONAL LIFE SCIENCE INSTITUTE

The International Life Sciences Institute (ILSI) presents itself as a group that is committed to "science for the public good" and to "improve planetary and human health and well-being in the 21st century".[160] ILSI is a corporate-funded non-profit organisation with 10 regional units worldwide.[161] It was founded by a former Coca-Cola vice president and has been funded for decades by companies such as Coca-Cola (until 2021),[162, 163] and Mars (until 2018)[164] and it currently includes companies such as Pepsi and the world's largest aspartame manufacturer Ajinomoto in its members.[165] Companies appear to benefit from the organisation's prolific publication of scientific studies that present their products and practices in a positive light and casually trivialise the potential health risks associated to their consumption.

ILSI Europe members: https://ilsi.eu/community/our-members/, screen shot from 07.01.2025

[160] https://ilsi.org/about/mission/
[161] https://ilsi.org/
[162] https://usrtk.org/pesticides/ilsi-is-a-food-industry-lobby-group/
[163] https://www.seattletimes.com/business/coca-cola-severs-longtime-ties-with-pro-sugar-industry-group/
[164] https://www.foodnavigator.com/Article/2018/02/08/Breaking-away-from-bad-science-Mars-to-leave-ILSI-in-transparency-bid
[165] https://ilsi.eu/community/our-members/

According to ILSI, the organisation published no less than 28 scientific publications and organised 63 workshops, conferences, and scientific meetings in 2023.[166] Numerous investigations carried out over the years by independent scientists, journalists and non-governmental organisations (NGOs) have shown that ILSI fiercely represents the interests of the food industry under the guise of an independent, scientific non-profit organisation and does not effectively promote measures to protect public health.[167, 168, 169, 170, 171]

The NGO U.S. Right to Know analysed over 15,000 pages of emails and documents obtained through freedom of information requests, revealing four patterns of influence by the group: funding research that aligns with industry interests, promoting industry-approved literature as independent, disseminating favourable information to policy makers, and suppressing dissenting opinions.[172] A Harvard researcher also revealed how Coca-Cola, via ILSI-China, influenced obesity policies by promoting physical activity over diet as the main cause, dominating research and public health strategies.[173]

ILSI public communication highlights that it is working for the protection of public health, but in reality, it seems to defend the profits of the food industry.

UNDISCLOSED INDUSTRY LINKS

At the 96th meeting of the JECFA in June/July 2023, 13 members and 13 supporting experts worked to derive a safe ADI for aspartame. All members and consulting experts declared beforehand that they had no overlapping industry links.[174] Articles published in French newspaper Le Parisien[175] and by the non-governmental organisation U.S. Right to Know[176] raise questions about such former and current industry links.

Six of the 13 members, including the chair and vice-chair, have been reported to have had previous ties with ILSI. These ties include participation

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[166] https://ilsi.org/
[167] Greenhalgh S (2019) Soda industry influence on obesity science and policy in China. J Public Health Pol 40:5–16. doi: 10.1057/s41271-018-00158-x
[168] https://www.nytimes.com/2019/09/16/health/ilsi-food-policy-india-brazil-china.html
[169] Steele S, Ruskin G, Stuckler D (2020) Pushing partnerships: corporate influence on research and policy via the International Life Sciences Institute. Public Health Nutrition 23(11): 2032–2040. doi:10.1017/S136898001900518
[170] https://corporateaccountability.org/wp-content/uploads/2020/09/Partnership-for-an-unhealthy-planet.pdf
[171] Maani N, Ruskin G, McKee M, Stuckler D. (2019) Public Meets Private: Conversations Between Coca-Cola and the CDC. Milbank Quarterly 97(1):74-90. doi: 10.1111/1468-0009.12368
[172] Steele S, Ruskin G, Stuckler D (2020) Pushing partnerships: corporate influence on research and policy via the International Life Sciences Institute. Public Health Nutrition 23(11): 2032–2040. doi:10.1017/S136898001900518
[173] Greenhalgh S (2019) Soda industry influence on obesity science and policy in China. J Public Health Pol 40:5–16. doi: 10.1057/s41271-018-00158-x
[174] https://cdn.who.int/media/docs/default-source/food-safety/jecfa/meetings/96th-jecfa-list-of-who-experts-participating-and-bios-2023.pdf?sfvrsn=78422bc8_3
[175] https://www.leparisien.fr/sciences/nouvelles-recommandations-sur-laspartame-les-liaisons-dangereuses-de-certains-experts-avec-coca-et-pepsi-19-07-2023-J3BYCFSOJJG7ZGHJEHFOVR5XFM.php
[176] https://usrtk.org/sweeteners/coca-cola-front-group-who-review-of-aspartame/

[Professor Ralph] Walton had seen that the conclusions of studies on the safety of aspartame were highly contradictory and wondered whether study outcome correlated with funding source. It did. NutraSweet, the maker of aspartame, funded seventy-four studies; all concluded that the sweetener was safe. But among nighty-two independently funded studies, eighty-four – more than 90 percent – questioned its safety.

Marion Nestle about a never-published review of research on the safety of aspartame (1996). Nestle M (2018) Unsavory Truth: How Food Companies Skew the Science of What We Eat. Basic Books, p. 37

in ILSI conferences,[177, 178] ILSI workshops,[179, 180, 181, 182] ILSI publications,[183, 184, 185, 186, 187] and ILSI task forces.[188] In addition, two supporting experts of the panel seem to still have links to ILSI at the time of writing this report.[189, 190, 191] These active links to ILSI were not previously declared. In response to journalists from Le Parisien, Fadéla Chaib, Team Lead of Department of Communications at WHO, declared regretting that the experts' links to ILSI were not sufficiently disclosed in the written declaration of interest or at the opening of the JECFA meeting.[192, 193] In 2015, the WHO already formally distanced itself from ILSI by classifying it as a "private entity" and terminating their official relationship.[194, 195]

This raises questions as to whether JECFA's judgment is as scientifically independent as the public is led to believe: Have past and current links to ILSI led to favouring industry-supported negative studies over independent positive studies? What would the JECFA ADI recommendation for aspartame look like without industry connections?

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[177] https://ilsi.eu/event/course-on-at-eurotox-2015-on-thresholds-of-toxicological-concern-basics-and-latest-developments/
[178] ILSI NA: The Importance of Exposure in Safety/Risk Assessments (Michael DiNovi) 2015; https://www.youtube.com/watch?v=Wv6ZW7_hqdE accessed 11.12.2024
[179] https://ilsi.eu/wp-content/uploads/sites/3/2016/06/Final-version-3-MCPD-esters.pdf
[180] https://hesiglobal.org/wp-content/uploads/sites/11/2016/06/Juberg.pdf
[181] Hammond B, Kough J, Herouet-Guicheney C, Jez JM (2013) Toxicological evaluation of proteins introduced into food crops. Crit Rev Toxicol. 43 Suppl 2(Suppl 2):25-42. doi: 10.3109/10408444.2013.842956
[182] https://www.efsa.europa.eu/sites/default/files/event/contam060403-m.pdf
[183] Benford D, Bolger PM, Carthew P, Coulet M, et al. (2010) Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic. Food Chem Toxicol. 48 Suppl 1:S2-24. doi: 10.1016/j.fct.2009.11.003
[184] https://ilsi.eu/wp-content/uploads/sites/3/2016/06/C2001Prin_Risk.pdf
[185] https://ilsi.eu/wp-content/uploads/sites/3/2016/06/C2000Acc_Dai.pdf
[186] Barlow S, Renwick AG,Kleiner J, Bridges JW, et al. (2006) Risk assessment of substances that are both genotoxic and carcinogenic: Report of an International Conference organized by EFSA and WHO with support of ILSI Europe. Food Chem Toxicol. 44(10):1636-50. doi: 10.1016/j.fct.2006.06.020
[187] Boobis A, Chiodini A,Hoekstra J, Lagiou P, et al. (2013) Critical appraisal of the assessment of benefits and risks for foods, 'BRAFO Consensus Working Group'. Food Chem Toxicol. 55:659-75. doi: 10.1016/j.fct.2012.10.028
[188] https://usrtk.org/wp-content/uploads/2023/07/DiNovi-EFSA-disclosure.pdf
[189] https://nc3rs.org.uk/sites/default/files/2022-03/David%20Lovell%20DOI%20Feb%202022.pdf
[190] https://ilsi.eu/scientific-activities/food-safety/threshold-of-toxicological-concern/
[191] https://biofortified.org/2012/10/14/ilsi-plant-composition/
[192] https://www.leparisien.fr/sciences/nouvelles-recommandations-sur-laspartame-les-liaisons-dangereuses-de-certains-experts-avec-coca-et-pepsi-19-07-2023-J3BYCFSOJJG7ZGHJEHFOVR5XFM.php
[193] https://usrtk.org/sweeteners/coca-cola-front-group-who-review-of-aspartame/
[194] https://www.theguardian.com/business/2023/aug/17/who-panel-aspartame-diet-coke-guidelines
[195] https://usrtk.org/wp-content/uploads/2018/07/ILSI-Official-Relations-WHO.pdf

5.3 SUMMARY: JECFA'S OPINION NO BASIS FOR CONFIDENCE

JECFA's assessment of aspartame appears to have prioritised industry-funded studies over independent research, resulting in a general dismissal of cancer concerns linked to the substance. The panel based its recommendations for a high Acceptable Daily Intake on outdated industry studies, while rejecting more recent independent research. Notably, these independent studies were key to IARC's classification of aspartame as "possibly carcinogenic to humans". Additionally, JECFA's panel members and supporting experts have past and ongoing ties to food industry lobby groups, further undermining the credibility of its conclusions. As a result, JECFA's recommendations on aspartame should not be trusted by consumers nor policy makers.

6 HEALTH FIRST: WHY ASPARTAME FAILS THE PRECAUTIONARY TEST

Independent research has uncovered significant evidence linking aspartame to cancer, while regulatory bodies like EFSA and JECFA have leaned heavily on industry-funded studies that – unsurprisingly – fail to show such risks. This raises a critical question: What should regulators do when faced with conflicting data? Is there enough evidence to justify a ban?

Aspartame would not be the first food additive to face restrictions or bans amidst scientific uncertainty, nor the first substance initially approved but later prohibited as advancements in research challenged its presumed safety. An interesting parallel can be drawn with potassium bromate, also known as E924, a chemical additive once widely used in bread-making to improve dough strength and texture. In 1990, the European Union banned its use in food under the precautionary principle, citing increasing concerns over its safety. Animal studies show clear links between potassium bromate exposure and various cancers, kidney damage and thyroid disease. In the 1980s, the International Agency for Research on Cancer (IARC) investigated the substance, and in 1999, it classified E924 as a Group 2B carcinogen, identifying it as "possibly carcinogenic to humans".[196]

A more recent case of precautionary action is the EU-wide ban on E171, or titanium dioxide. It is a white pigment and food additive widely used in products like candies, baked goods, and chewing gum to enhance appearance. However, due to safety concerns, the EU banned its use as a food additive in 2021.[197] EFSA's scientific opinion points to the impossibility of ruling out concerns about genotoxicity (the ability of a substance to damage DNA, which can cause mutations leading to cancer) and remaining uncertainties to confidently rule out health risks.[198]

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[196] https://usrtk.org/chemicals/potassium-bromate/; https://inchem.org/documents/iarc/vol40/potassiumbromate.html

[197] https://www.efsa.europa.eu/en/efsajournal/pub/6585

[198] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2021.6585

By the time the EU banned the substance for use as a food additive, IARC had already classified the substance as a Group 2B carcinogen ("possibly carcinogenic to humans"),[199] and it was officially designated as a suspected carcinogen under inhalation for some powder forms under EU law (category 2 carcinogen under the EU regulation on the classification, labelling, and packaging of chemicals, the CLP regulation). This EU classification, based on a dossier submitted by French authorities, had recently come into effect following a prolonged regulatory battle during which industry groups attempted to undermine the process.[200] Meanwhile, the French government had already enacted a national suspension of titanium dioxide in food additives based on a scientific opinion from the French Health and Safety Agency ANSES that raised health concerns and pointed to important data gaps for the completion of a full safety assessment.[201] In a similar way, the European Commission concluded that EFSA's inability to rule out risks justified a precautionary ban.[202] This EU-wide ban took effect in 2022.

Both cases provide a potential precedent for aspartame, which IARC has similarly classified as 2B: "possibly carcinogenic to humans".

6.1 THE PRECAUTIONARY PRINCIPLE IN EUROPEAN FOOD LAW

As the recent case of E171 shows, the EU is allowed to ban and has already banned substances even in the face of uncertainty about health risks. The legal basis for such action often is the precautionary principle.

This principle is a cornerstone of European environmental and health policy. It comes into play when scientific data are incomplete or uncertainties exist, but there are indications of potential risks. Unlike reactive measures that address harm after it occurs, the principle advocates for preventive action before risks are fully confirmed. However, its interpretation is the subject of ongoing debate. As highlighted in a report for the European Parliament, there are varying approaches: a weaker interpretation is often used to resist regulation, and a stronger one is employed to justify decisive action.[203]

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[199] https://monographs.iarc.who.int/list-of-classifications

[200] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2020.044.01.0001.01.ENG; https://corporateeurope.org/en/2019/06/toxic-lobbying-titanium-dioxide-label-debate-continues; https://www.env-health.org/wp-content/uploads/2018/06/20180606-letter-on-titanium-dioxide.pdf

[201] https://www.economie.gouv.fr/dgccrf/laction-de-la-dgccrf/les-enquetes/dioxyde-de-titane-dans-les-denrees-alimentaires-tout-doit; https://www.anses.fr/en/content/food-additive-e171-anses-reiterates-its-recommendations-consumer-safety

[202] https://ec.europa.eu/newsroom/sante/items/732079/en

[203] https://www.europarl.europa.eu/RegData/etudes/IDAN/2015/573876/EPRS_IDA(2015)573876_EN.pdf p. 12-13

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In the EU, the precautionary principle has been enshrined since the Treaty on the European Union (or Maastricht Treaty, 1992) and is explicitly mentioned in Article 191 of the Treaty on the Functioning of the European Union (TFEU). The article states that EU environmental policy shall be based on the precautionary principle.[204]

In the General Food Law of the EU, the precautionary principle is explicitly codified in **Regulation (EC) No 178/2002**, which lays down the general principles and requirements of food law and establishes the European Food Safety Authority (EFSA). Article 7 of this regulation specifically addresses the precautionary principle, stating that when the possibility of harmful effects on health is identified but scientific uncertainty persists, risk management measures may be adopted to ensure a high level of health protection.[205] These measures are intended to be provisional and are subject to review as new scientific data becomes available.

[204] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:12012E/TXT
[205] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002R0178

Art. 7 (1) General Food Law (Regulation 178/2002)

"In specific circumstances where, following an assessment of available information, the possibility of harmful effects on health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment."

In a 2000 communication, the European Commission outlined the precautionary principle as a vital tool for protecting public health and the environment when scientific uncertainty exists. This communication is often seen as a guideline on how to apply the principle in practice.[206]

First of all, the Commission requires a comprehensive risk analysis from the European Food Safety Authority (EFSA). The identified risks must be substantiated and not merely hypothetical – a criterion that aspartame clearly meets (as discussed in Chapter 4).

Secondly, the European Commission's Communication outlines key principles for precautionary measures. These measures must be **proportional**, avoiding unrealistic "zero-risk" goals but allowing for bans in cases of significant uncertainty. They should be **non-discriminatory** and **consistent**, aligning with measures in similar cases with adequate scientific data. Measures should be **provisional** and subject to review as new scientific evidence emerges, ensuring ongoing research and adaptation. Lastly, the **burden of proof** for demonstrating safety is placed on the manufacturer.[207]

Finally, a **cost-benefit analysis** is recommended, considering both economic and non-economic impacts, but health protection always takes precedence over economic factors:

> "In the conduct of such an examination, account should be taken of the general principle and the case law of the Court that the protection of health takes precedence over economic considerations."[208]

In other words, the extensive use and economic significance of a substance must take a back seat if health risks are deemed sufficiently plausible. This general interpretation of the precautionary principle is also reflected in the ban of E171 (see above), where a widely used substance was banned in the face of scientific uncertainty.

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[206] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2000:0001:FIN:en:PDF
[207] De Smedt K, Vos E (2022) The Application of the Precautionary Principle in the EU in The Responsibility of Science, ed. by H.A. Mieg, Springer, p. 168-169. doi: http://dx.doi.org/10.1007/978-3-030-91597-1_8
[208] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2000:0001:FIN:en:PDF

6.2 HOW EUROPEAN COURTS INTERPRET THE PRECAUTIONARY PRINCIPLE

As the EU Commission already indicates in the last quote, it is also necessary to have a look at the Court of Justice of the European Union (CJEU) and its interpretation of the precautionary principle.

The court has consistently affirmed the precautionary principle as a fundamental component of EU law, highlighting its importance in safeguarding public health and the environment.

As part of a large case law, in the landmark case **Pfizer Animal Health v. Council (C-13/99)**, the court upheld the EU's decision to ban antibiotics used as growth promoters in animal feed. Despite ongoing scientific uncertainties, the court determined that the precautionary principle warranted action to address potential health risks, such as antibiotic resistance, even in the absence of definitive evidence. This ruling reinforces the criteria and application of the precautionary principle as outlined by the European Commission.[209] It states that:

> "In case of scientific uncertainty as to the existence of a risk to human health, the EC institutions as well as the Member States may invoke the precautionary principle in order to adopt protective measures, in spite of the fact that a proper risk assessment showing conclusive scientific evidence cannot be conducted."[210]

In 2022, an EU-funded research project analysed all 147 references made to the precautionary principle between 2000 and 2019 in court rulings.[211] Two conclusions from their research are worth noting here at length.

First, the researchers argue that in "various cases, the courts have accepted the use of the precautionary principle in the absence of proper scientific evidence" and go on to explain that:

> " [T]he courts ruled that the possibility of a risk, the absence of zero risk, or the lack of information establishes uncertainty and risk, and is therefore sufficient legal basis for precautionary measures."[212]

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[209] Case T-13/99, Pfizer Animal Health SA v. Council, 'Pfizer', 2002. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:61999TJ0013&from=EN

[210] De Smedt K, Vos E (2022) The Application of the Precautionary Principle in the EU in The Responsibility of Science, ed. by H.A. Mieg, Springer, p. 178 doi: http://dx.doi.org/10.1007/978-3-030-91597-1_8

[211] De Smedt K, Vos E (2022) The Application of the Precautionary Principle in the EU in The Responsibility of Science, ed. by H.A. Mieg, Springer doi: http://dx.doi.org/10.1007/978-3-030-91597-1_8

[212] De Smedt K, Vos E (2022) The Application of the Precautionary Principle in the EU in The Responsibility of Science, ed. by H.A. Mieg, Springer, p. 183 doi: http://dx.doi.org/10.1007/978-3-030-91597-1_8 , emphasis added.

Second, they conclude that "it seems that in most cases the courts agree with a ban or upholds restrictions. It seems that the courts generally adopt a moderate to strong interpretation of the precautionary principle."[213]

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[213] De Smedt K, Vos E (2022) The Application of the Precautionary Principle in the EU in The Responsibility of Science, ed. by H.A. Mieg, Springer, p. 184 doi: http://dx.doi.org/10.1007/978-3-030-91597-1_8

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6.3 CONCLUSION: A LONG OVERDUE BAN

Lessons learned so far:

- **Toxicological studies**, like those by the Ramazzini Institute, have shown dose-dependent increases in lymphomas, leukaemias, and other cancers in rodents, even at exposure levels close to those experienced by humans.
- **Epidemiological studies**, such as the INSERM and Schernhammer studies, highlight associations between aspartame consumption and increased risks of cancers, including non-Hodgkin's lymphoma and breast cancer.
- Since recent independent studies have already found **potential cancer associations at much lower doses of aspartame** than the EFSA and JECFA recommendations – for example between half a can and a can per day of a diet soda – the precautionary principle should apply.
- In **2023**, the **International Agency for Research on Cancer (IARC)** classified aspartame as "possibly carcinogenic to humans" (Group 2B), based on a comprehensive review of epidemiological, toxicological, and mechanistic evidence.
- Recent research indicates that aspartame may be associated with a range of **other health concerns**, including heart disease, type 2 diabetes, and neurological damage.

This recent IARC assessment easily qualifies as a robust piece of evidence about aspartame's cancer hazard to be subsequently considered by European decision makers in their risk analysis and warrants the application of a precautionary approach. As generally known, the assessment of risk is the combination of the assessment of the hazard and the exposure. The IARC hazard assessment shows that cancer concerns arising from aspartame use cannot be dismissed. On the other hand, real-life exposure to the substance is significant due to its wide use in food products, starting with soft drinks. **Therefore, it is impossible to entirely dismiss the health risks associated with the consumption of this substance, and the criteria for applying the precautionary principle are clearly met.**

The risk evaluations from **JECFA** and, most notably, **EFSA** concluded that aspartame poses no harm to consumers, while **IARC** concluded a possible cancer hazard arising from aspartame. Partly, the bodies looked at different aspects: IARC focused on the intrinsic properties of the substance (does the substance inherently have the capacity to cause cancer?), while JECFA and EFSA focused on the probability that the hazard occurs. As detailed earlier, the case is further complicated by the different approaches of the bodies towards the scientific evidence available, with inconsistencies and apparent bias in the JECFA and EFSA assessments, which heavily rely on industry-funded research.

Consequently, these JECFA and EFSA evaluations cannot be taken as definitive reassurance. Instead, their weaknesses strengthen the argument for invoking the precautionary principle. Simply put, further independent research is needed to conclusively rule out aspartame's health risks. Should this prevent decision makers from taking action based on the existing knowledge of potential health risks? Absolutely not.

Finally, would a ban be proportionate? Considering precedents with other substances, even a potential cancer risk provides more than enough justification for regulatory action, including the ban of aspartame.

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