

**Summary of findings of the evaluation of aspartame at the
International Agency for Research on Cancer (IARC) Monographs Programme's
134th Meeting, 6–13 June 2023
and
The JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)
96th meeting, 27 June–6 July 2023**

IARC evaluation

An *IARC Monographs* working group of 25 independent experts from 12 different countries, all assessed as free from conflicts of interest, was convened in Lyon on 6–13 June 2023. They reviewed all studies that have been published or made publicly available related to cancer in humans and in experimental animals, and to mechanistic evidence regarding the key characteristics of carcinogens. These studies were reviewed according to the strict scientific process described in the [Preamble to the *IARC Monographs*](#).

The [working group](#) classified aspartame as *possibly carcinogenic to humans* (Group 2B) based on *limited* evidence for cancer in humans (for hepatocellular carcinoma, a type of liver cancer). Among the available cancer studies in humans, there were only three studies on the consumption of artificially sweetened beverages that allowed an assessment of the association between aspartame and liver cancer. In these studies, consumption of artificially sweetened beverages was considered a good proxy for aspartame exposure, as supported by evidence on the country and time period of aspartame use in beverages. In all three studies, a positive association was observed between consumption of artificially sweetened beverages and risk of liver cancer, either overall or in important subgroups of the studied populations, but chance, bias or confounding could not be ruled out as an explanation for the positive findings.

There was also *limited* evidence for cancer in experimental animals. There was an increased incidence of tumours in two species, mouse and rat, of both sexes seen in three published studies. However, based on concerns over the study design, interpretation and reporting of data, the working group concluded that the evidence for cancer in experimental animals was *limited*.

In addition, there was *limited* mechanistic evidence that aspartame exhibits key characteristics of carcinogens, based on consistent and coherent evidence that aspartame induces oxidative stress in experimental systems and suggestive evidence that aspartame induces chronic inflammation and alters cell proliferation, cell death and nutrient supply in experimental systems.

A summary of the evaluation, together with a short rationale, will be published online in *The Lancet Oncology* on 14 July (at 00:30 CEST). The complete evaluation will be published in Volume 134 of the *IARC Monographs*.

JECFA evaluation

The JECFA panel, composed of 13 members and 13 experts from 15 countries, all screened and found to be free of conflict of interest, was convened in Geneva on 27 June–6 July 2023.

Overall, the Committee concluded that there was no convincing evidence from experimental animal or human data that aspartame has adverse effects after ingestion. This conclusion is underpinned by the information that aspartame is fully hydrolysed in the gastrointestinal tract into metabolites that are identical to those absorbed after consumption of common foods, and that no aspartame enters the systemic circulation as such. The Committee concluded that the data evaluated during the meeting indicated no reason to change the previously established acceptable daily intake (ADI) of

0–40 mg/kg body weight for aspartame. The Committee therefore reaffirmed the ADI of 0–40 mg/kg body weight for aspartame.

Following oral exposure, aspartame is fully hydrolysed in the gastrointestinal tract of humans and animals into three metabolites: phenylalanine, aspartic acid and methanol. The Committee therefore reaffirmed that there is no systemic exposure to aspartame after dietary exposure. Phenylalanine, aspartic acid and methanol are also released from commonly consumed foods by enzymatically catalysed hydrolysis. The Committee noted that in oral aspartame exposure studies in humans at doses up to the current ADI, there were no increases in the plasma concentrations of the metabolites of aspartame.

Aspartame has been tested in several in vitro and in vivo genotoxicity assays. Considering the conflicting results and the limited quality of the studies, the committee concluded that aspartame does not perform a genotoxic action. The committee evaluated data from 12 oral carcinogenicity studies of aspartame and identified limitations in all of them. The Committee noted that all the studies apart from those by Soffritti et al. (2005; 2006; 2007; 2010) showed negative results¹. The Committee considered the positive findings of Soffritti and colleagues, noting however that there were limitations in the study design, execution, reporting and interpretation of these studies.

Based on the results of the oral carcinogenicity studies of aspartame, the absence of evidence of genotoxicity, and a lack of evidence on a mechanism by which oral exposure to aspartame could induce cancer, the Committee concluded that it is not possible to establish a link between aspartame exposure in animals and the appearance of cancer.

The Committee evaluated data from randomized controlled trials (RCTs) and epidemiological studies to examine the association between aspartame consumption and certain health effects, such as cancer, type 2 diabetes (T2D) and other non-cancer health endpoints in humans.

The Committee noted that statistically significant increases were reported for some cancers, such as hepatocellular, breast and haematological (non-Hodgkin lymphoma and multiple myeloma) cancers, in some cohort studies conducted with aspartame or beverages containing aspartame as an intense sweetener. However, a consistent association between aspartame consumption and a specific cancer type could not be demonstrated. All the studies had limitations in how they estimate exposure, especially the ones that used non sugar sweeteners exposure as proxy for aspartame exposure. Reverse causality, chance, bias and confounding by socioeconomic or lifestyle factors, or consumption of other dietary components, could not be completely ruled out.

A summary of the evaluation, together with a short rationale, will be published online on the WHO and FAO JECFA webpage on 14 July. The JECFA 96th meeting report and *Monographs* will be published within 6 months.

The role of IARC and JECFA in chemical substance evaluation

¹ Soffritti, M., Belpoggi, F., Degli Esposti, D., Lambertini, L. (2005) Aspartame induces lymphomas and leukaemias in rats. *Eur. J. Oncol.*, 10, 107-116

Soffritti, M., Belpoggi, F., Degli Esposti, D., Lambertini, L., Tibaldi, E., Rigano, A., (2006). First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. *Environ. Health Perspect.* 114, 379–385. <https://doi.org/10.1289/ehp.8711>

Soffritti, M., Belpoggi, F., Tibaldi, E., Esposti, D.D., Lauriola, M. (2007). Life-span exposure to low doses of aspartame beginning during prenatal life increases cancer effects in rats. *Environ. Health Perspect.* 115, 1293–1297. <https://doi.org/10.1289/ehp.10271>

Soffritti, M., Belpoggi, F., Manservigi, M., Tibaldi, E., Lauriola, M., Falcioni, L., Bua, L. (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.* 53,1197–1206. <https://doi.org/10.1002/ajim.20896>

- IARC and JECFA have different but complementary roles in the assessment of chemical substances.
- IARC focuses on cancer as an outcome and undertakes hazard identification, which is the first fundamental step to understanding carcinogenicity. Hazard identification aims to identify the specific properties of the agent and its potential to cause harm, i.e. the potential for an agent to cause cancer, looking at both dietary and non-dietary exposures.
- On 6–13 June 2023 a working group met to evaluate the carcinogenicity of aspartame for the first time at the *IARC Monographs Meeting 134* in Lyon, France.
- JECFA considers all possible health impacts and undertakes a risk assessment, which determines the probability that a specific type of harm (e.g., cancer and other noncommunicable diseases, impaired reproductive health, impaired physical and mental development, etc.) will occur under certain conditions and levels of exposure. A risk assessment is based on the identified hazard properties of an agent and anticipated exposures in specific scenarios. Thus, all dietary, conditions, frequency and levels of exposure are considered. JECFA's role is specifically to perform a risk assessment for the dietary exposure scenario.
- When evaluating the safety of chemical substances, JECFA uses all available data and evaluations including the *IARC Monographs* hazard identification.
- At the 96th JECFA meeting, which took place on 27 June – 6 July 2023, aspartame was re-evaluated. The last evaluation was done in 2016. IARC had informed the Committee about the discussions, key deliberations, and the outcome of the carcinogenic hazard of aspartame at its 134th meeting in June 2023, in confidence. In addition, to ensure consistency in the approach taken by the two expert panels, three JECFA members participated as observers in the IARC Monograph meeting and the IARC and JECFA Secretariats attended both the IARC and JECFA meetings.

WHO relationship with IARC and JECFA

IARC has a unique dual position as an independent international cancer research institute, and as the specialized cancer research agency of the World Health Organization (WHO) within the United Nations system, established in May 1965 by a resolution of the World Health Assembly. IARC is governed by its own Governing Council and its Scientific Council; the former comprises representatives from each Participating State, plus the WHO Director-General. IARC has its own defined scientific methods as set by the Preamble to the IARC Monographs. More information about IARC governance can be found here: https://www.iarc.who.int/cards_page/organization-and-management/.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an international scientific expert committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). It has been meeting since 1956, initially to evaluate the safety of food additives. Its work now also includes the evaluation of contaminants, naturally occurring toxicants, and residues of veterinary drugs in food. More information about JECFA can be found here: [https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-\(jecfa\)/about](https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa)/about)

FAQs

What are the results of IARC's hazard identification?

An *IARC Monographs* working group (WG) of 25 independent experts from 12 different countries – all assessed as free from conflicts of interest – was convened in Lyon on 6–13 June 2023. The WG reviewed all publicly available data according to the strict scientific process described in the [Preamble to the IARC Monographs](#).

The working group classified aspartame as **possibly carcinogenic to humans (Group 2B)** on the basis of:

Limited evidence for cancer in humans, based on findings for liver cancer (specifically, hepatocellular carcinoma). Among the available cancer studies in humans, there were only three studies on the consumption of artificially sweetened beverages that allowed an assessment of the association between aspartame and liver cancer. The three studies (which included four large cohorts) were conducted within the European Prospective Investigation of Cancer and Nutrition (EPIC) cohort,² a pooled analysis of the National Institutes of Health (NIH)-American Association of Retired Persons (AARP) cohort and the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) cohort,³ and the Cancer Prevention Study (CPS)-II cohort.⁴ In these studies, consumption of artificially sweetened beverages was considered a proxy for aspartame exposure, as supported by evidence on the country and time period of aspartame use in beverages. In all three studies, a positive association was observed between consumption of artificially sweetened beverages and risk of liver cancer, either overall or in important subgroups of the studied populations, but bias or confounding could not be ruled out as an explanation for the positive findings.

There was also **limited evidence** for cancer in experimental animals. There was an increased incidence of malignant neoplasms or a combination of benign and malignant neoplasms in two species (mouse and rat) of animals of both sexes seen in three published studies. However, based on concerns over the study design, the working group concluded that the evidence for cancer in experimental animals was **limited**. Specifically, in the analyses in the two prenatal exposure studies, no adjustments were made for litter effects (e.g., number of litters, pups per treatment group, etc.), which could lead to false positive results if pups from the same litter responded in the same way to treatment because of genetic factors. Concerns were also expressed regarding diagnoses of lymphomas (predominantly, but not exclusively, those located in the lung). Also, there were unresolved questions on the interpretation of the histology of hepatocellular proliferations and bronchioloalveolar lesions.

In addition, there was **limited mechanistic evidence** that aspartame exhibits key characteristics of carcinogens, based on consistent and coherent evidence that aspartame induces oxidative stress in experimental systems and suggestive evidence that aspartame induces chronic inflammation and alters cell proliferation, cell death, and nutrient supply in experimental systems. There were some positive findings in several studies available for genotoxicity; however, many had limitations in study design, data analysis, and interpretation.

A summary of the evaluation, together with a short rationale, is being published online in *The Lancet Oncology*.⁵ The complete evaluation will be published in Volume 134 of the *IARC Monographs*.

² Stepien M, Duarte-Salles T, Fedirko V, Trichopoulou A, Lagiou P, Bamia C, et al. (2016). Consumption of soft drinks and juices and risk of liver and biliary tract cancers in a European cohort. *Eur J Nutr*. 55(1):7–20. <https://doi.org/10.1007/s00394-014-0818-5> PMID:25528243

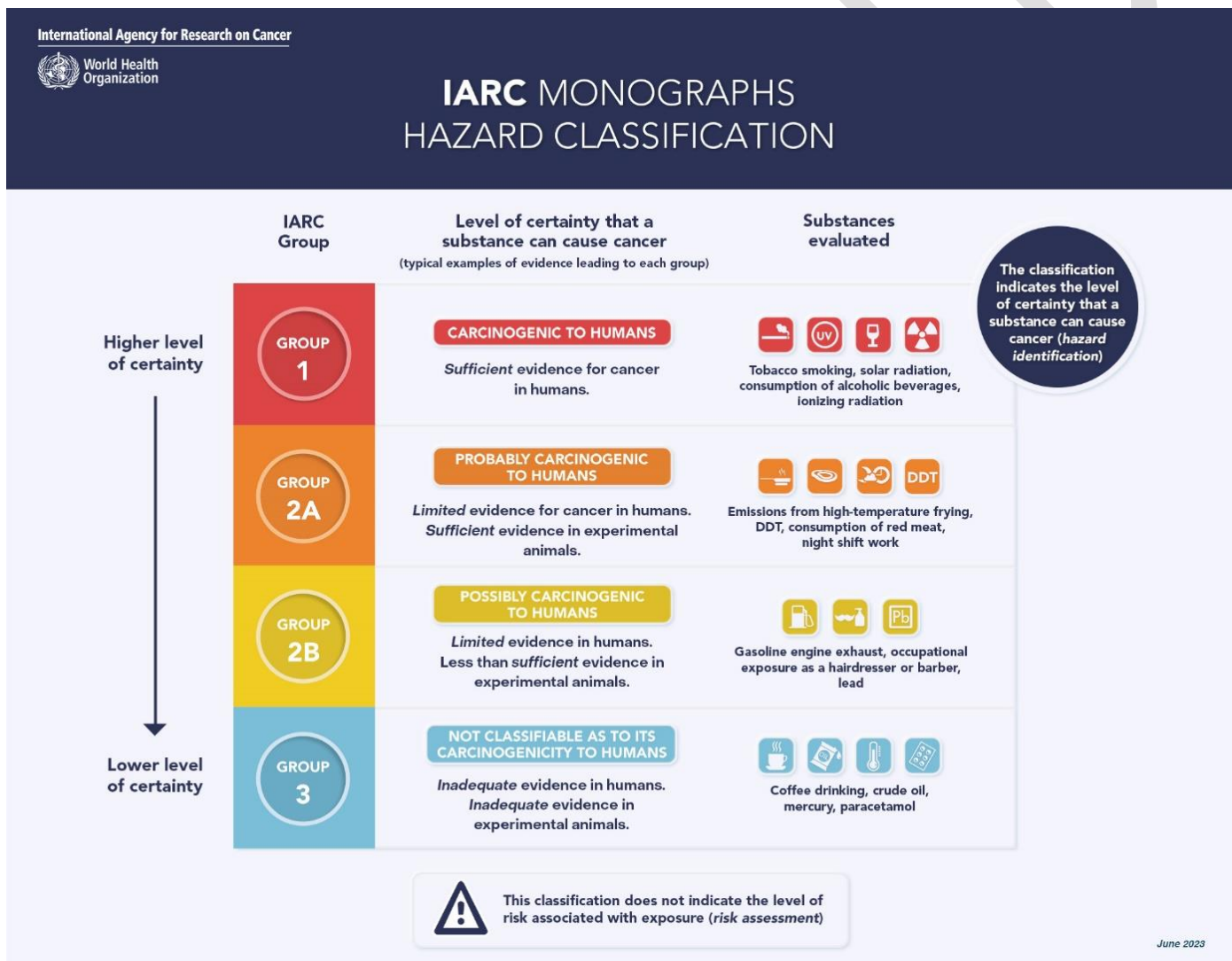
³ Jones GS, Graubard BI, Ramirez Y, Liao LM, Huang WY, Alvarez CS, et al. (2022). Sweetened beverage consumption and risk of liver cancer by diabetes status: a pooled analysis. *Cancer Epidemiol*. 79:102201. <https://doi.org/10.1016/j.canep.2022.102201> PMID:35728406

⁴ McCullough ML, Hodge RA, Campbell PT, Guinter MA, Patel AV (2022). Sugar- and artificially-sweetened beverages and cancer mortality in a large U.S. prospective cohort. *Cancer Epidemiol Biomarkers Prev*. 31(10):1907–18. <https://doi.org/10.1158/1055-9965.EPI-22-0392> PMID:36107009

⁵ Riboli et al. (2023). Carcinogenicity of aspartame, isoeugenol, and methyleugenol. *Lancet Oncol*, Published online 23:30 BST July 13, 2023. [https://doi.org/10.1016/S1470-2045\(23\)00341-8](https://doi.org/10.1016/S1470-2045(23)00341-8).

What does a cancer hazard classification in Group 2B mean?

The *IARC Monographs* cancer hazard identification indicates the strength of evidence that an agent can cause cancer in humans. A Group 2B classification means that the agent has been classified as *possibly carcinogenic to humans*. A classification in Group 2B can be reached when there is *limited* evidence that the agent could cause cancer in humans, but *limited* or *inadequate* evidence for cancer in experimental animals; or when there is convincing (*sufficient*) evidence that the agent causes cancer in experimental animals but little or no information (*inadequate* evidence) about whether it causes cancer in humans; or when there is *strong* mechanistic evidence, showing that the agent exhibits one or more of the recognized key characteristics of human carcinogens.



What does the IARC classification indicate?

The *IARC Monographs* classifications reflect the strength of the scientific evidence as to whether an agent can cause cancer in humans, but they do not indicate the degree of risk of developing cancer at a given exposure

level or with a given route of exposure. The types of exposure, the extent of risk, the people who may be at risk, and the cancer types linked with the agent can be very different across agents.

Since the IARC Group indicates the strength of the evidence regarding a cancer hazard and not the cancer risk at a given level of exposure, the cancer risk (at typical exposure levels) associated with two agents classified in the same IARC Group may be very different.

How are these classifications used? Can IARC enforce regulations based on these classifications?

IARC is a research organization that evaluates evidence on the causes of cancer but does not make health recommendations. Health and regulatory agencies may include *IARC Monographs* evaluations in their consideration of actions to prevent exposure to potential carcinogens. IARC does not recommend regulations, legislation, or public health interventions, which remain the responsibility of individual governments and other international organizations.

How many studies were evaluated in the IARC assessment of aspartame?

More than 7000 references were collected and screened. Approximately 1300 studies were included in the review and made available to the working group.

What types of study were eligible for review by the IARC Working Group and where did they come from?

As described in the current [Preamble to the IARC Monographs](#) (last revised in 2019), the Working Group reviews publicly available scientific data, such as peer-reviewed papers in the scientific literature, and may also review unpublished reports, if made available in their final form by governmental agencies and if they contain enough detail for critical review. In the case of aspartame, the working group was able to consult and review literature derived from the *Call for Data* in 2011 for the European Food Safety Authority (EFSA) risk assessment, which was made available and accessible on the [EFSA website](#). In addition, IARC opened a public *Call for Data* on its website 1 year ahead of the meeting for Volume 134. Eligible studies are only those published or accepted for publication in the openly available scientific literature by the time of the working group meeting.

Has the IARC Monographs programme previously evaluated food additives?

Over the course of its 51-year history, the *IARC Monographs* programme has evaluated over 70 different substances that have been or are used as food additives. Examples include the first sweetener dulcin, evaluated in 1968, as well as cyclamates, d-limonene, coumarin, the artificial sweetener saccharin, quinoline, mineral oils, and many others.

Why has IARC decided to evaluate aspartame?

An independent advisory group of international experts makes recommendations concerning which agents suspected to cause cancer should be evaluated by the *IARC Monographs* programme. Agents are recommended for evaluation when there is evidence that people may be exposed and when there is also scientific evidence available that may lead to a determination of carcinogenicity (or probable or possible carcinogenicity).

In 2019, the Advisory Group to Recommend Priorities for the *IARC Monographs* recommended a wide variety of agents or substances for a new or updated evaluation by the *IARC Monographs* programme during 2020–2024. These agents may have different impacts on public health. The food additive aspartame was accorded high priority for evaluation by the *IARC Monographs* programme based on emerging cancer evidence in humans and in laboratory animals.

A working group evaluated the carcinogenicity of aspartame for the first time at the *IARC Monographs* Meeting 134, which took place on 6–13 June 2023 in Lyon, France.

What are the differences between JECFA and IARC's evaluations?

In the *IARC Monographs* programme, IARC undertakes hazard identification, which is the first fundamental step to understanding carcinogenicity. Hazard identification aims to identify the specific properties of the agent and its potential to cause harm, i.e., the potential for an agent to cause cancer.

The JECFA programme undertakes risk assessment, which determines the probability that a specific type of harm (e.g., cancer, reproductive toxicity, genotoxicity) will occur under certain conditions and levels of exposure. As such, it is based on the identified hazard properties of an agent and the anticipated exposures in specific scenarios, thus considering the routes, conditions, frequency, and levels of exposure. JECFA specifically performs a risk assessment for the dietary exposure scenario since it evaluates food additives.

How do the methodologies used differ between these evaluations?

IARC and JECFA evaluate different types of evidence. IARC only considers publicly available studies and reports. JECFA considers all publicly available studies and reports and may also consider studies conducted for regulatory purposes.

For aspartame, there was a large degree of overlap regarding publicly available studies and reports, because the *IARC Monographs* Working Group was able to consider many unpublished studies that had been made publicly available by the European Food Safety Authority (EFSA).

IARC assesses carcinogenic hazard through the evaluation of evidence regarding cancer in humans and in animals and mechanistic evidence on exposures to a variety of different agents. In an *IARC Monographs* evaluation, evidence may derive from occupational, environmental, nutritional and other exposures that people may experience. *IARC Monographs* evaluations are conducted according to strict criteria, as described in the recently revised [Preamble to the IARC Monographs](#). JECFA performs a risk assessment for the dietary exposure scenario because it evaluates food additives.

Did IARC work with JECFA on these hazard and risk evaluations?

The two evaluations are independent. The *IARC Monographs* programme and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) have distinct roles, working group members, and rules and principles governing the evaluations of hazard and risk. However, in the case of aspartame, the two secretariats followed

side-by-side the progress of the evaluation, informed each other about the data available, and had shared membership.

Moreover, to ensure consistency in the approach taken by the two expert panels, three members of the JECFA participated as observers in the IARC Monograph meeting and the IARC and JECFA secretariats attended both the IARC and the JECFA meetings.

Why are the evaluations by IARC and JECFA complementary?

The IARC working group assessed the potential carcinogenic effect of aspartame, while JECFA updated its previous risk assessment exercise, which included reviewing the current acceptable daily intake (ADI) and doing a dietary exposure assessment for aspartame. The sequence of these evaluations and the close collaboration between the *IARC Monographs* secretariat and the JECFA secretariat permitted a comprehensive evaluation of the health effects of aspartame consumption based on the latest available evidence.

Why did IARC and JECFA release the results together?

Given the availability of new research results, aspartame was recommended as a high priority for evaluation both by the Advisory Group to Recommend Priorities for the *IARC Monographs* and by the Codex Committee on Food Additives (CCFA) of substances proposed for evaluation by JECFA. IARC assessed the potential carcinogenic effect of aspartame (hazard identification), while JECFA updated its risk assessment, including reviewing the acceptable daily intake, and evaluated dietary exposure.

The evaluations are complementary and were conducted one after the other in the months of June and July 2023.

Are the JECFA conclusions consistent with the IARC classification?

JECFA based their conclusions on a qualitative synthesis of different pieces of evidence that can be summarised as follows:

- Limited evidence for cancer in humans: Both the IARC working group and JECFA noted and reviewed the available cancer studies in human. The IARC working group and JECFA noted the observed statistically significant increases for liver cancer (specifically, hepatocellular carcinoma), however, reverse causality, chance, bias and confounding by socioeconomic or lifestyle factors, or consumption of other dietary components cannot be ruled out. JECFA uses the term “not convincing” instead of “limited” evidence as used in the *IARC Monographs* programme.
- A study in France involving approximately 100 000 participants during 2009–2021 (NutriNet-Sante) observed an increase in health risks when lower consumers (mean: 3.24 mg/day; SD: 4.06) and higher consumers (mean: 47.42 mg/day; SD: 60.75) are compared with non-consumers of aspartame (Debras et al., 2022, 2023). Statistical associations were seen at exposures 20 or 40 times lower than the current ADI.
- There was also limited evidence for cancer in experimental animals. Both the IARC working group and JECFA have noted similar limitations in the positive animal studies (the Ramazzini Institute studies).
- There was also limited mechanistic evidence. Both the IARC working group and JECFA analysed aspartame's possible mechanisms (IARC) or modes of action (JECFA). Studies exploring genotoxicity were considered

inconclusive by JECFA and by IARC due to limitations in design. However, the IARC evaluation identified consistent and coherent evidence of oxidative stress and suggestive evidence of chronic inflammation and of alteration of cell proliferation, cell death, or nutrient supply, all in experimental systems.

- Furthermore, both JECFA and IARC noted that aspartame is fully hydrolysed in the gastrointestinal tract into metabolites that are common to those absorbed after consumption of other foods and drinks. No aspartame enters the systemic circulation as such.

Conclusions are expressed differently in line with the requirements of the respective mandates.

The IARC evaluation noted limitations in all three streams of evidence (human cancer, cancer in experimental animals, and mechanistic evidence). The “limited” evidence of hepatocellular carcinoma in humans is what led to the Group 2B evaluation, in accordance with the Preamble to the IARC Monographs.

Unlike IARC, JECFA does not have a classification system. JECFA have not found convincing evidence of a plausible mechanism leading to adverse effects in animals or humans nor a sufficient number of studies demonstrating such effects.

What about non-cancer effects?

JECFA, unlike IARC, explores adverse effects other than cancer. Recent data from a well-conducted cohort study showing a statistical association between aspartame consumption and type 2 diabetes, and aspartame consumption and cerebrovascular disease, were not considered convincing by JECFA. Although the associations persisted in various sensitivity analyses designed to limit confounding and the possibility of reverse causation, certain biases inherent to cohort studies and the possibility of residual confounding cannot be eliminated. To infer that the association is causal, epidemiologists use a number of criteria such as strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy. At present, it is difficult to satisfy all or part of these criteria. These associations require further research to make firm conclusions.

Are there other mechanisms of action not addressed by JECFA?

Research in animals and humans has suggested the possibility that aspartame may alter the microbiome. However, results are inconsistent, and the mechanism by which this might possibly be linked to outcomes observed in human epidemiological studies is unclear. One randomized controlled trial in humans found that aspartame consumption functionally altered the oral and gut microbiomes. Although aspartame did not significantly alter glycaemic responses in study subjects themselves, germ-free mice receiving bacterial transplants from these subjects displayed impaired glycaemic responses. Results of this study also suggest the possibility of interpersonal variability in responses to aspartame. Further research is needed to understand the role that alterations in the microbiome may play in possible health effects of aspartame consumption.

The IARC evaluation found that relevant studies in rodents showed that exposure to aspartame increased insulin serum levels. Although these findings suggest alteration of insulin sensitivity, their relevance to mechanisms of carcinogenesis is a notable research gap.

Is WHO recommending additional research on aspartame ?

Yes, IARC and WHO encourage independent research groups to develop better conducted cohort studies (including longer follow-up and repeated dietary questionnaires in existing cohorts) and randomized controlled trials, including studies of mechanistic pathways relevant to insulin regulation, metabolic syndrome, and diabetes, particularly as related

to carcinogenicity . Additional studies of carcinogenicity in experimental systems may also be helpful to elucidate whether there is a carcinogenic hazard posed by aspartame consumption.

What is WHO recommending on the consumption of sugars and non-sugar sweeteners?

In both adults and children, WHO recommends reducing the intake of free sugars to less than 10% of total energy intake (strong recommendation). WHO suggests a further reduction of the intake of free sugars to below 5% of total energy intake (conditional recommendation).

[WHO suggests that non-sugar sweeteners not be used not be used as a means of achieving weight control or reducing the risk of noncommunicable diseases \(conditional recommendation\)](#). WHO reaffirms its recommendation to not use non-sugar sweeteners as a means of achieving weight control or reducing the risk of noncommunicable diseases as the evidence still suggests that their use does not help with long-term weight control and may increase risk of type 2 diabetes, cardiovascular diseases and premature mortality.