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Aspartame Safety Review by the WHO: a Short Story about a Tempest in a Teapot…

Article By:

Christophe Leprêtre

On July 14, 2023, the World Health Organization (WHO) announced the results of the dual review of the well-known sugar-substitute aspartame by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the International Agency for Research on Cancer (IARC), two scientific bodies with different missions, but with one common parent: the WHO. Both bodies, within their own jargon and scoring system, essentially concluded (despite the appearances) that aspartame itself likely does not raise safety concerns beyond what the science has been telling about this sweetener since its first evaluation in 1981. JECFA reaffirmed the same level for the acceptable daily intake (ADI) as the one established in 1981, which is also the same as the one reaffirmed by the European Food Safety Authority (EFSA) in 2013. IARC used some indirect and not-causal statistical analysis from human general cohorts to conclude that the substance is "possibly carcinogenic (2B) to humans — classification 2(B), the second lowest of the four classifications on the IARC scale. This article discusses additional aspects of this dual review of aspartame, which IARC reviewed for a single hazard (carcinogenicity, in contrast to JECFA, which reviewed broader evidence on a variety of health endpoints.

The Facts

JECFA

At this 96th JECFA meeting held at the end June – early July 2023, JECFA completed a full evaluation of all biochemical, toxicological, and epidemiological
studies available on aspartame since the substance was first reviewed by the Committee in 1981, including the review of the safety of aspartame metabolites and degradation products. Given that the full JECFA96 report will not be available until the end 2023, it is important to refer to JECFA conclusions as stated by this Joint FAO/WHO Expert Meeting on food safety risk assessment of Food Additives:

- JECFA reaffirmed the long-standing ADI — up to 40 mg per kg body weight per day for aspartame.[1]
- JECFA concluded that there is no concern for genotoxicity of oral exposure to aspartame.
- JECFA concluded that there is no concern for carcinogenicity in animals from oral exposure to aspartame.

- JECFA concluded that aspartame is not a reproductive or developmental toxicant in animals.[2]
- JECFA also assessed – for the first time – estimates of the dietary exposure to aspartame and concluded that dietary exposure to aspartame does not pose a health concern, based on up-to-date use level data in foods as well as more advanced data about food consumption levels. JECFA noted that these dietary exposure estimates do not exceed the ADI.
- JECFA reaffirmed that there is no systemic exposure to aspartame after dietary exposure, given that following oral exposure, aspartame is fully hydrolysed in the gastrointestinal tract of humans and animals into three metabolites: phenylalanine, aspartic acid, and methanol. Indeed, JECFA noted that phenylalanine, aspartic acid, and methanol are also released from commonly consumed foods by enzymatically catalysed hydrolysis, and that after the pre-systemic hydrolysis of aspartame, these substances enter the systemic circulation at levels lower than those derived from consumption of common foods.[3]
- JECFA concluded that the evidence of an association between aspartame consumption and cancer in humans is not convincing by reviewing several recently published studies that investigated possible mechanisms that may be relevant to the induction of cancer, including oxidative stress (i.e., the exact same mechanistic studies reviewed also by IARC) for two main reasons: (a) the studies reporting changes in markers of oxidative stress had limitations in their design and (b) histopathological changes observed that would normally be expected from a prolonged exposure to oxidative stress were not observed in other short- and long-term toxicity studies of aspartame.
- JECFA concluded that the evidence of an association between aspartame consumption and cancer in humans is not convincing after reviewing the same randomized controlled trials (RCTs) and epidemiological studies of the association between aspartame consumption and certain health effects, such as cancer, type 2 diabetes (T2D), and other non-cancer health end-points in humans as were reviewed by IARC. JECFA noted that all studies have limitations with respect to their assessment of exposure, particularly with respect to aspartame versus intense sweeteners in general. JECFA experts noted that reverse causality, chance, bias, and confounding by socioeconomic or lifestyle factors, or consumption of other dietary components could not be ruled out.[4]
- JECFA concluded that the evidence of an association between aspartame consumption and evaluated non-cancer health end-points (such as type-2 diabetes) is not convincing due to inconsistent results[5].[6]
- Overall, JECFA concluded that there was no convincing evidence from experimental animal or human data that aspartame has adverse effects after ingestion.

IARC

IARC conclusions were reached at its 134th monograph meeting held earlier in June 2023. The executive summary of this IARC group review is included in a published article in the journal *Lancet Oncology*.[7] In a nutshell, IARC concluded as follows:

- IARC classified aspartame as *possibly carcinogenic* to humans (IARC Group 2B)[8].
- IARC classified aspartame based on:
    - “limited” evidence for cancer in humans, based on findings for liver cancer (specifically, hepatocellular carcinoma)[9], while noting that “*bias or confounding could not be ruled out as an explanation for the positive findings*” as well as that in “*these studies, consumption of artificially sweetened beverages was considered a proxy for aspartame exposure*”;
    - “limited” evidence for cancer in experimental animals, mostly referring to the same

    - studies published by Sofritti *et al*. that JECFA and EFSA reviewed as well;[10] *and*,
    - "limited" mechanistic evidence.[11]
- IARC full report will be published towards the end of the year in Volume 134 of the IARC Monographs.
- Immediately following IARC's meeting on cancer hazard identification, JECFA conducted a risk assessment exercise, including a review of the acceptable daily intake of aspartame.

What people said about them

WHO Officials

"Cancer is one of the leading causes of death globally. Every year, 1 in 6 people die from cancer. Science is continuously expanding to assess the possible initiating or facilitating factors of cancer, in the hope of reducing these numbers and the human toll," said Dr Francesco Branca, Director of the Department of Nutrition and Food Safety at WHO. *"The [IARC and JECFA] assessments of aspartame have indicated that, while safety is not a major concern at the doses which are commonly used, potential effects have been described that need to be investigated by more and better studies,"* Dr Branca further added. *"We're not advising consumers to stop consuming (aspartame) altogether, (…), we're just advising a bit of moderation", Source: WHO*

"The findings of limited evidence of carcinogenicity in humans and animals, and of limited mechanistic evidence on how carcinogenicity may occur, underscore the need for more research to refine our understanding on whether consumption of aspartame poses a carcinogenic hazard," said Dr Mary Schubauer-Berigan, Head of the IARC Monograph Programme.

About IARC, *"we need better studies with longer follow-up and repeated dietary questionnaires in existing cohorts. We need randomized controlled trials, including studies of mechanistic pathways relevant to insulin regulation, metabolic syndrome and diabetes, particularly as related to carcinogenicity,"* said Dr Moez Sanaa, Head of the Standards and Scientific Advice on Food and Nutrition Unit at WHO. *"JECFA also considered the evidence on cancer risk, in animal and human studies, and concluded that the evidence of an association between aspartame consumption and cancer in humans is not convincing,"* Dr Sanaa further added. *Source: WHO*

The Sweetener Industry

"JECFA has once again reaffirmed aspartame's safety after conducting a thorough, comprehensive and scientifically rigorous review," said ISA Secretary General Frances Hunt-Wood. *"Aspartame, like all low/no-calorie sweeteners, when used as part of a balanced diet, provides consumers with choice to reduce sugar intake, a critical public health objective."*

"To put this in context, IARC's 2B classification puts aspartame in the same category as kimchi and other pickled vegetables. IARC would be the first to say that they don't suggest people should stop using kimchi at meals. As part of its comprehensive assessment, reconfirming the safety of aspartame, JECFA examined IARC's conclusions and found no concern for human health. Importantly, IARC is not a food safety body and its 2B classification does not consider intake levels nor actual risk, making an IARC review far less comprehensive than the thorough reviews conducted by food safety bodies like JECFA and potentially confusing for consumers."
Source: www.sweeteners.org

The Soft Drink Industry

"This definitive conclusion by the world's leading health and food safety experts once again affirms that aspartame is safe. After rigorous review, this landmark WHO and FAO finding further strengthens confidence in the safety of aspartame and will play a vital role in informing consumers as they consider all options to reduce sugar and calories in their diets. JECFA's comprehensive conclusion that aspartame is safe builds on the overwhelming weight of scientific evidence for more than four decades, as well as positive determinations by food safety authorities in more than 90 countries," commented ICBA Executive Director Kate Loatman.

"IARC, which is not a food safety agency, has now officially conceded that aspartame poses no more of a hazard than aloe vera and hundreds of other substances that it places in the same category based on evidence IARC itself describes as 'limited' and 'less than sufficient. While IARC's leaked opinion may have needlessly confused consumers with sensational speculation, IARC has already deferred to the WHO and FAO joint expert committee [JECFA] – which just once again found aspartame safe – as the appropriate global authority to comprehensively assess the safety of consuming aspartame." Source: https://www.icba-net.org/

The Chewing Gum Industry

"The results of JECFA's review mean that aspartame – one of the most thoroughly researched food ingredients in history – is considered by experts to be a safe food additive at currently permitted levels. Low and no-calorie sweeteners (LNCS), including aspartame, are among the most thoroughly researched food ingredients."

"Unlike sugar(s) and like other LNCS, aspartame does not promote tooth decay because it cannot be broken down by oral bacteria in the mouth. Furthermore, chewing sugar-free chewing gum stimulates saliva which helps to maintain healthy teeth by clearing the mouth of food debris and sugar(s), neutralizing harmful plaque acids, and supporting remineralization of tooth enamel. The use of sugar-free chewing gum to promote and support oral health and reduce the risk of dental caries has been recognized by leading governmental authorities." Source: https://www.gumassociation.org/index.cfm/icga-views/

The Campaigners

"Anyone who now believes that Diet Coke is a healthy thirst quencher is mistaken. Even if aspartame poses no immediate health risk when consumed in normal quantities: The WHO classifies the substance as possibly carcinogenic and points out the insufficient study situation," said Manuel Wiemann, Campaigner at Foodwatch. *Source: Foodwatch website.*

Academics

David Spiegelhalter, an emeritus statistics professor at Cambridge University, told the Associated Press that the guidance means that *"average people are safe to drink up to 14 cans of diet drink a day … and even this 'acceptable daily limit' has a large built-in safety factor."*

Tom Sanders, a professor emeritus of nutrition and dietetics at King's College London, criticised the guidance for not taking into account "the real-world

situation," particularly in the field of dietetics. *"Sometimes what you're trying to do is get people to control their weight, which is to reduce their calorie intake, and it can help if people are drinking a full sugary drink to switch to a reduced-calorie drink or zero-calorie drink,"* he explained to Euronews Next.

David Klurfeld, a nutrition expert at the Indiana University School of Public Health-Bloomington. *"The dose makes the poison,"* said Klurfeld, who previously served on an IARC panel. *"Even essential nutrients like vitamin A, iron and water will kill you within hours if too much is consumed." Source: Euronews Next*

Next Possible Steps

JECFA

In addition to its risk assessment (and reaffirmation of the ADI), JECFA made several modifications to the specifications identity and purity for aspartame (amended already twice since 1981). JECFA:

- updated the description to include details on manufacturing;
- added flavour enhancer to the functional uses;
- replaced the method of assay with a high-performance liquid chromatography method;
- added a test and specification for "other related impurities"; *and*
- removed the test and specification for "other optical isomers".

The outcome of the risk assessment and the revised specifications both will be considered by the global food additive safety regulators at the next meeting of the Codex alimentarius Committee on Food Additives to be held in April 2024 (see CCFA webpage at https://www.fao.org/fao-who-codexalimentarius/committees/committee/related-meetings/jp/?committee=CCFA*)*

IARC

The work of IARC stops there on aspartame, at least until further scientific data becomes available to confirm or change it. IARC will discuss in March 2024 its work program for the next five years, and it may discuss whether it should rather focus its scarce resources on "agents" which are more important in terms of proven carcinogens and therefore could arguably justify higher priorities in terms of key public health concerns.

IARC also could delegate such tasks to JECFA, as well as national or regional risk assessment bodies around the world, to perform sound risk assessments and adopt risk management measures, where warranted. In some specific jurisdictions, there may be additional reviews of the IARC work (e.g., California Proposition 65).).

Other

It is also reasonable to expect the worldwide nutrition-ist community to steer the sweeteners food additives topic through various means, from dietary recommendations to nutrition profiling systems, which may be leading to nutritional scoring of foods, warning statements, taxation, or other disincentive policies or campaigns.

Main sources:

[1] WHO press release on aspartame (July 13, 2023): https://www.who.int/news/item/14-07-2023-aspartame-hazard-and-risk-assessment-results-released

[2] Lancet Oncology – Summary of IARC Monograph 134 on aspartame: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00341-8/fulltext (subject to registration)

[3] FAO/WHO JECFA Executive Summary of 96th meeting: https://www.fao.org/3/cc6908en/cc6908en.pdf

[1] *Remark (note of the author): that ADI means that a human of "typical" body weight – generally 70 Kg for an adult) could consume up to nearly 3000 milagrams per day – during a whole life – without fearing any toxicological health concern. Foods sweetened with aspartame typically contain from a few hundred to a few dozen micrograms of aspartame. Consumption of such foods would not, under any foreseeable circumstance lead to anything close to such ADI. To put things in perspective, JECFA's ADI established for Steviol glycosides is one-tenth that of Aspartame (i.e., 4 mg per kg bw per day).*

[2] *The no-observed-adverse-efect-level (NOAEL) in one- or two-generation reproductive and developmental toxicity studies in rats was 4000 mg per kg bw per day, the highest dose tested. The NOAEL for developmental toxicity in mice was 5700 mg per kg bw per day, the highest dose tested.*

[3] *These conclusions were 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.*

[4] *JECFA 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, JECFA noted that a consistent association between aspartame consumption and a specific cancer-type was not observed.*

[5] *RCTs showed reduced glycaemic responses after aspartame consumption, whereas in epidemiological studies aspartame consumption was associated with a greater T2D risk. JECFA also noted that the results of the epidemiological studies may be biased by how T2D cases were identified (either specific medications and self-reported physician diagnosis).*

[6] *Note of the author: it echoes, to some extent, the conclusions of the WHO NUGAG experts about a lack of sufficiently convincing evidence about the consumption of non-sugar sweeteners, which led the WHO to conclude only with a conditional recommendation to overall limit to a reasonable level the consumption of non-sugar sweeteners (class to which aspartame belongs).*

[7] *See* https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00341-8/fulltext

[8] *See IARC's Cancer Grading Scale, from "certain" (Class 1) to "Cannot classify" (Class*

3)
at https://www.iarc.who.int/wp-content/uploads/2023/06/IARC_MONO_classifcation_2023_updated.png

[9] 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, 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, and the Cancer Prevention Study (CPS)-II cohort. 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.

Note of the author: it should be noted that the study quoted as the EPIC study above was co-authored by a researcher from INSERM who attended the IARC Monograph 134 expert group meeting, as an expert expected to assess the results of that study.

[10] In those controversial studies reviewed, "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."

Note of the author: Aspartame has been on the IARC Monograph work program since 2014, mostly driven by a few controversial studies published by Sofritti et. (Ramazzini Institute) since 2000. These are the same studies which had been dismissed on several occasions when EFSA reviewed them in the period 2006-2013. EFSA conclusions were clear-cut: these studies are not in line with current protocols to assess food safety and some of their raw results were questionable. More at EFSA website at https://www.efsa.europa.eu/en/topics/topic/aspartame. It should also be noted that one representative of the laboratory who led those controversial studies by the European Ramazzini Foundation attended the IARC Monograph 134 expert group meeting, as an expert expected to assess the results of those studies.

[11] IARC Monograph 134 expert group stated that published studies suggest 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."

Note of the author: it seems therefore that IARC experts came to the same conclusions as JECFA experts about the significant limitations in the study design, data analysis, and interpretation.

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