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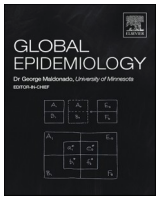

Commentary

Perspectives on recent reviews of aspartame cancer epidemiology

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A B S T R A C T

Aspartame is a dipeptide non-sugar sweetener that was first marketed in the US in carbonated beverages in 1983, before gaining prominence globally. The Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) and the WHO International Agency for Research on Cancer (IARC) completed evaluations of aspartame and cancer in July 2023. JECFA reaffirmed the safety of aspartame, stating that epidemiology evidence is "not convincing," and that there are no consistent associations between aspartame and cancer (JECFA/IARC, 2023; JECFA, 2023). JECFA also noted "reverse causality, chance, bias and confounding by socioeconomic or lifestyle factors, or consumption of other dietary components, could not be completely ruled out" in relevant epidemiology studies (JECFA/IARC, 2023). In contrast, IARC stated that there are three "high quality" studies on liver cancer (Riboli, 2023), but that the evidence is limited because "chance, bias or confounding could not be ruled out as an explanation for the positive findings" (JECFA/IARC, 2023). IARC does not provide an explanation as to how these studies can be both high quality and have these weaknesses, most notably potential exposure misclassification, or how inconsistent associations from studies with these weaknesses constitute limited evidence. Further, when IARC concludes an agent has limited or inadequate human evidence (and no sufficient animal or strong mechanistic evidence), it classifies that agent as either Group 2B, a possible human carcinogen, or Group 3, not classifiable as to its carcinogenicity. Ultimately, the interpretations of Group 2B and Group 3 classifications are intended to be similar. However, a Group 2B designation may make it appear to scientists and non-scientists alike that the evidence is pointing in the direction of causality. This can lead to unnecessary confusion with respect to the evidence, as well as a perception of a disagreement within WHO regarding aspartame. This apparent contradiction could have been avoided by assigning the IARC classification most consistent with the conclusion that the human evidence for cancer is inadequate: Group 3.

1. Introduction

Aspartame is a dipeptide that is one of several non-sugar sweeteners (NSSs) added to foods and beverages. It was first used in carbonated beverages in 1983 [1], before becoming a global phenomenon in the years that followed. Aside from saccharin, aspartame was the sole NSS in carbonated beverages in the US until 1998, when sucralose and acesulfame potassium were approved for use in carbonated beverages [2,3].

To date, around two dozen prospective cohort studies and approximately twice as many case-control studies have assessed associations between NSSs and various cancers [4]. Very few observational studies have assessed aspartame specifically, but it has been assumed that aspartame was the primary NSS consumed in some studies based on the period of time during which dietary exposures were ascertained. Many of these studies were considered by the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group in a 2022 review that evaluated health outcomes associated with NSSs consumption [5], based on studies published through July 2021. WHO [5] reported that there were no consistent associations between NSSs, including aspartame, and any cancer type, and that the certainty of the evidence for all cancer types was "very low."

While the 2022 report assessed several NSSs, two other WHO bodies completed evaluations of aspartame in July 2023: the WHO International Agency for Research on Cancer (IARC) and a committee administered by the Food and Agriculture Organization of the United Nations (FAO) and WHO, called the Joint FAO/WHO Expert Committee on Food Additives (JECFA) [6–8]. Both these evaluations considered studies published after July 2021 in addition to those considered by WHO [5].

Consistent with the 2022 WHO evaluation, JECFA concluded "the evidence of an association between aspartame consumption and cancer in humans is not convincing" [7]. In contrast, IARC concluded that aspartame is a possible human carcinogen (Group 2B) [6,8], based on three studies that it determined provided "limited evidence for cancer in humans": Stepien et al. [9], Jones et al. [10], and McCullough et al. [11]. IARC stated, "All three studies were of high quality and controlled for many potential confounders. However, the Working Group concluded that chance, bias, or confounding could not be ruled out with reasonable confidence in this set of studies. Thus, the evidence for cancer in humans was deemed 'limited' for hepatocellular carcinoma and 'inadequate' for other cancer types" [8]. This characterization is consistent with IARC's

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definition of "limited evidence" in humans as occurring when "A causal interpretation of the positive association observed in the body of evidence on exposure to the agent and cancer is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence." [12]. However, IARC does not provide an explanation for how studies can be considered credible or of high quality if chance, bias, and confounding cannot be ruled out.

Further, one of IARC's definitions of "inadequate evidence regarding carcinogenicity" is human data that are "of poor quality or informativeness" [12]. IARC does not provide any guidance as to how one should differentiate evidence for which chance, bias, or confounding cannot be ruled out (i.e., limited evidence) from evidence that is of poor quality or informativeness (i.e., inadequate evidence). Notably, the studies on which IARC based its conclusions for aspartame have similar weaknesses as those for other cancer types IARC appropriately concluded were inadequate. A conclusion of "inadequate evidence regarding carcinogenicity" in humans would have resulted in a Group 3 (i.e., the lowest) classification for aspartame, which means that aspartame would have been "not classifiable as to its carcinogenicity to humans" [12]. This would have been consistent with conclusions of WHO in 2022, JECFA in 2023, and other recent reviews that the human data are of poor quality and therefore do not provide limited evidence of a causal association, but rather inadequate evidence on which to base a causal determination [4–7].

To help address issues with confidence in the evidence, Goodman et al. previously identified a few key study quality domains that should always be considered in epidemiology studies evaluating aspartame and cancer, i.e., potential exposure misclassification, outcome misclassification, confounders/covariates, and selection bias [13]. Recall bias is minimized in cohort studies in general, but NSS cohort studies still potentially suffer from significant exposure misclassification. Most cohort studies assessed dietary consumption only once at baseline or a few times over the course of the study. Most studies also did not have information on aspartame specifically, so assumptions that exposure to NSSs were a proxy for aspartame may not have been correct. No study could totally dismiss chance findings, residual confounding (particularly for well-known risk factors), unmeasured confounding, or the potential for reverse causality. According to Boffetta et al. [14], residual confounding and unmeasured confounding are often downplayed in epidemiology studies but can generate effect estimates on the order of 1.5–2.0, which is higher in magnitude than are commonly reported in NSS/aspartame cancer epidemiology studies. Finally, while most studies used robust measures for outcome assessment, some studies inappropriately combined cancers with different etiologies or had insufficient follow-up to account for cancer latency.

1.1. 2023 IARC review

IARC concluded that evidence for cancer in humans is "inadequate" for all cancer types except hepatocellular carcinoma (HCC) [8], for which it concluded evidence is "limited." IARC indicated that a positive association was observed in three studies [9–11] "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" [6]. IARC stated that artificially sweetened beverages were a good proxy for aspartame exposure in these studies [6,8].

While there were a few positive associations in these studies, they were not consistent either within or across studies. Stepien et al. reported a very small association overall (although it's unclear whether this was based on fully adjusted models), and stated that the association was attenuated and weak in individuals without diabetes [9]. Jones et al. found associations in people with diabetes within 6 years of follow up, but not longer, and not in people without diabetes [10]. McCullough et al. only found a statistically significant trend in non-smoking men, but only when analyses were not adjusted for body mass index (BMI) [11]. Even if these studies were to be considered methodologically robust (i.e., high quality), their inconsistent findings do not provide convincing or even limited evidence for an association. In addition, as described below, these studies should be considered to be "of poor quality or informativeness," mostly due to issues with potential exposure misclassification. All three of these cohort studies would have benefited from repeated questionnaires, which would have allowed exposures and other time-varying covariates to be modeled based on more complete information. These studies and their strengths and weaknesses, particularly with respect to liver cancer analyses, are described below and summarized in Table 1.

1.2. Stepien et al. (2016)

Stepien et al. evaluated whether HCC, intrahepatic bile duct (IHBC), and biliary tract cancer (GBTC) hazards were associated with "combined soft drinks (sugar- and artificially-sweetened)" and juices in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort of 477,206 participants from 10 European countries [9]. A strength of this study is that it evaluated HCC, IHBC, and GBTC separately, which is more appropriate than combining all liver cancers with different etiologies together. The study also followed a large number of participants from a range of European countries with diverse diets. The authors analysed exposure to artificially sweetened beverages (ASBs) generally. At baseline (in 1992) participants were asked whether they drank sugar-sweetened beverages (SSBs) or ASBs in the 12 months prior, which, as noted above, could have resulted in exposure misclassification. Cancer cases were identified through 2010 from national cancer registries, national health insurance records, contact with cancer or pathology registries, and active follow up.

The authors identified 191 HCC (22 in individuals with diabetes), 66 IHBC, and 236 GBTC cases, and reported results for ASBs and HCC [9], indicating all other ASB results were not statistically significant. They reported that overall each additional serving of ASB was associated with a small increased risk of HCC (Hazard Ratio [HR] = 1.06, 95% Confidence Interval [CI]: 1.03–1.09), and noted that, "When only non-diabetic individuals were studied, the HRs were similar to whole cohort estimates, but weaker." There was no adjustment for hepatitis B and C infections, cirrhosis, or non-alcoholic fatty liver disease (well known risk factors for HCC), and information on other potential confounders was collected only at baseline. Other soft drink HRs discussed in this study were presented both as crude estimates and adjusted for confounders, and many HRs discussed in the text were qualified with "after adjustment for confounders," but the authors only presented this single HR for ASBs and HCC, and did not state whether it was adjusted or not.

Stepien et al. stated [9]:

> Participants who developed HCC were mainly men, older, physically active, less educated, and were more likely to have prevalent diabetes and gallstones, to be current smokers, and to be former or current heavy drinkers than the non-cases. They also had higher BMI and waist-to-hip ratio… Both daily consumers of soft drinks and juices were characterized by less healthy dietary pattern than non-consumers (higher consumption of sugar and confectionary, cakes and biscuits, and lower intake of legumes, fruits and vegetables, fish and shellfish)… Self-reported diabetic subjects were more likely to consume daily artificially than sugar-sweetened soft drinks (5.5 vs. 1.9%, respectively).

These differences between cases and non-cases and the lack of information on whether the ASB HR for HCC was adjusted makes it difficult to interpret the results. Indeed, the authors stated that their results [9]:

> may imply that: i) components other than sugar present in diet/reduced-sugar soft drinks, such as sweetening agent or colorants, could be associated with the risk of HCC; ii) artificially-sweetened

Table 1
Study Quality Assessments for Four Cohort Studies of Aspartame and Cancer. Because of study weaknesses, IARC and JECFA concluded that chance, bias, and confounding cannot be ruled out as explanations for any reported associations in these studies [6–8].

Citation	Cohort(s)	Exposure Assessment	Outcome Assessment	Confounding/Covariate Consideration	Study population
Stepien et al. (2016)	EPIC	Strengths • Consumption frequency ascertained Weaknesses • Self-reported • Baseline assessment only • Asked about consumption for past 12 mos • ASB not specific to aspartame • Artificially-sweetened foods (and tabletop sweeteners) not considered	Strengths • Evaluated HCC, IHBC, and GBTC separately • Up to 11.4 years of follow-up Weaknesses • No major weaknesses	Strengths • For "soft drinks (SSB + ASB)": Adjusted for smoking, alcohol, BMI, physical activity, education, and diabetes in some analyses Weaknesses • Information on confounders were only collected at baseline • Did not adjust for hepatitis B and C infections, cirrhosis, non-alcoholic fatty liver disease, or total caloric intake • Unclear whether reported ASB-specific associations were adjusted for potential confounders, including SSB consumption or diabetes • Potential residual confounding	Strengths • Large study population (n = 477,206; 464,688 without diabetes and 12,518 with diabetes) • Cohort recruited from several EU Member States with diverse diets • Exposed and non-exposed participants drawn from the same cohort Weaknesses • >11% of the cohort was excluded from the analysis • No information on differences between included and excluded individuals
Jones et al. (2022)	NIH-AARP, PLCO	Strengths • At time of dietary data collection, aspartame was likely primary NSS in ASBs • Frequency of ASB consumption determined Weaknesses • Self-reported • Baseline assessment only • Artificially-sweetened foods (and tabletop sweeteners) not considered	Strengths • Cases confirmed through linkage to state registries (NIH-AARP and PLCO) or medical record review (PLCO) • Up to 24 years of follow-up (median 12 years) Weaknesses • PLCO cohort cases identified via self-report	Strengths • Adjusted for age at baseline, sex, race/ethnicity, BMI, smoking, alcohol use, study, total energy intake Weaknesses • Potential residual confounding • Did not adjust for SSB consumption, activity level, or family history of cancer • Information in PLCO cohort only collected at baseline, ≤5 years prior to dietary assessment • Self reported diabetes, no distinction between type 1 and 2 • Information only collected once (at baseline or at time of dietary assessment)	Strengths • Large combined cohort of 553,874 participants (506,389 without diabetes and 47,485 with diabetes) • Large number of primary liver cancer cases (839 individuals without and 221 individuals with diabetes) • Exposed and non-exposed participants drawn from the same cohort Weaknesses • Limited information on study recruitment and attrition • >30% of PLCO cohort excluded • No information on differences between included and excluded individuals
McCullough et al. (2022)	CPS-II	Strengths • Included both consumption of ASBs and tabletop NSS packet intake • Frequency of ASB consumption determined Weaknesses • Consumption data ascertained prior to regulatory approval of aspartame in carbonated beverages • Baseline assessment only	Strengths • Deaths linked to death certificates or NDI • Up to 34 years of follow-up Weaknesses • Unclear whether ascertainment of deaths was complete through 1988	Strengths • Adjusted for age, sex, race/ethnicity, smoking, marital status, education, and red and processed meat, fruit and vegetable, alcohol, and SSB consumption Weaknesses • Did not control for early adulthood BMI, total caloric intake or diabetes diagnosis after baseline • Some analyses not adjusted for BMI • Potential residual confounding	Strengths • Large study population(n = 934,777) • Exposed and non-exposed were drawn from the same cohort Weaknesses • >20% of participants excluded • No information on differences between included and excluded individuals

(*continued on next page*)

Table 1 (*continued*)

Citation	Cohort(s)	Exposure Assessment	Outcome Assessment	Confounding/Covariate Consideration	Study population
Debras et al. (2022)	NutriNet-Santé Study	Strengths • Included participants were surveyed every 6 mos on 3 non-consecutive 24-h days (random 2 weekdays and 1 weekend day) for 2 yrs, with at least 2 completed surveys • Food products linked to three databases to estimate NSS and aspartame exposures in food, beverages, and tabletop packets; potential reformulations considered Weaknesses • Self-reported • Appears to be baseline assessment only • A large portion of the participants only completed 2 or 3 records out of a possible 15 within the baseline period (nearly ½ of non-consumers and more than $^{1}/_{3}$ of consumers) • Unclear how complete 24-h dietary exposure data were (mean = 5.6 measurements/person)	Strengths • Self-reported cases verified by medical records or participants' physicians. • Unreported cases identified via linkage to national health insurance system and mortality registry Weaknesses • Cancers were combined for evaluation (e.g., all cancers, obesity-related cancers, breast cancer) • Relatively short follow-up time (median = 7.8 yrs)	Strengths • Adjusted for age, sex, BMI, education, percentage of weight gain, physical activity, number of dietary records, smoking, family history of cancer, diabetes, energy intake without alcohol, daily intakes of alcohol, sodium, saturated fatty acids, fiber, sugar, fruit, vegetables, whole-grain foods, and dairy products, and acesulfame-K and sucralose intake • For breast cancer, also adjusted for age at menarche, age at first child, number of biological children, menopausal status, oral contraceptive use, and hormonal treatment for menopause Weaknesses • Potential residual confounding • Uncontrolled confounding possible in combined cancer analysis	Strengths • Exposed and non-exposed participants drawn from the same cohort • Large study population (n = 102,865), including 1,776 individuals with diabetes Weaknesses • 15.6% of the participants excluded • No information on differences between included and excluded individuals • Population recruited online and was mostly female

Notes: AARP = American Association of Retired Persons; ASB = Artificially Sweetened Beverage; BMI = Body Mass Index; CPS-II = American Cancer Society's Cancer Prevention Study II; EPIC = European Prospective Investigation into Cancer and Nutrition; GBTC = Biliary Tract Cancer; HCC = Hepatocellular Carcinoma; Hr = Hour; IHBC = Intrahepatic Bile Duct; Min = Minimum; Mos = Months; NDI = National Death Index; NIH = National Institutes of Health; NSS = Non-Sugar Sweetener; PLCO = Prostate, Lung, Colon, Ovary Screening Trial; SSB = Sugar Sweetened Beverage; Yrs = Years.

beverages, in general considered as healthier since they do not contain sugar, could be more frequently consumed by individuals with some existing underlying disorders, for example diabetes or obesity, and iii) diabetes/obesity might have been a consequence of high intake of sugary drinks in the past.

We also note that, in addition to only collecting data on exposure at one point in time, the authors said that they were not able to distinguish the type of artificial sweetener used in beverages, which they acknowledged "made it difficult to assess the effect of…[the] type of artificial sweetener used on the diet-disease relationship" [9]. At the time of data collection, several sweeteners had been approved [15], so no conclusions should be drawn regarding aspartame specifically. The authors also noted that the small number of HCC cases made it possible that the ASB finding was due to chance. Notably, Jones et al. [10] highlighted that this study did not distinguish between those with or without diabetes.

1.3. Jones et al. (2022)

Jones et al. conducted a prospective study using pooled data from both the NIH-AARP Diet and Health Study (NIH-AARP), and the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial, to evaluate the association between sweetened beverages and primary liver cancer [10]. The pooled cohort included 553,874 individuals: 506,389 who did not have diabetes, and 47,485 who did (based on self-report). The NIH-AARP baseline questionnaires were mailed between 1995 and 1996, and included questions about frequency (but not volume) of "potentially aspartame-containing" diet drink consumption in the last 12 months [16]. The PLCO diet history questionnaire was administered in 1998 [17], and included questions about the frequency (but not the volume) of consumption of both SSBs and ASBs including soda, fruit punches, and fruit juices. The large size of the cohort is a major strength of this study, as is the adjustment for several key confounders in analyses. Also, at the time of baseline dietary collection, aspartame was most likely the primary sweetener in beverages marketed in these US-based cohorts [1–3].

The authors found no associations between artificially-sweetened beverages and primary liver cancer in people without diabetes [10]. They also found no statistically significant associations among individuals with diabetes with >12 years of follow up (ASB HR = 0.82, 95% CI: 0.64–1.05; artificially-sweetened soda HR 0.78, 95% CI: 0.59–1.03; artificially-sweetened fruit punch HR = 1.01, 95% CI: 0.61–1.69). In contrast, the authors reported small statistically significant associations in individuals with diabetes during the first 12 years of follow up: sweetened beverages overall (SSB and ASB combined) (HR: 1.12, 95% CI: 1.01–1.24), ASB (HR = 1.13, 95% CI: 1.02–1.25), soda overall (sugar and artificially sweetened combined) (HR = 1.13, 95% CI: 1.00–1.26), and artificially sweetened soda (HR = 1.13, 95% CI: 1.01–1.27). In analyses stratified by years of follow up (0 to ≤6 years, 6 to ≤12 years, 12 to ≤18 years, and over 18 years) for "all sweetened beverages" (ASB and SSB combined, but primary consumption was ASBs), an association was only reported during the first 6 years of follow up (HR = 1.20, 95% CI: 1.04–1.38; HR = 1.06, 95% CI: 0.92–1.02; HR = 0.77, 95% CI: 0.57–1.00; and HR not calculated [0 cases], respectively).

The lack of associations in people without diabetes and those with diabetes with over 6 years of follow up suggests reverse causation as a possible explanation for statistically significant findings among individuals with diabetes with 6 or fewer years of follow up, particularly when considering that people diagnosed with diabetes may switch to ASBs to control blood sugar [18]. The association may also be due to misinformation on beverage consumption or a confounding factor, or it may be a chance finding. If ASBs were associated with an increased liver cancer risk, even only among those with diabetes, one would expect the association to persist and be stronger with longer follow up, but it does not.

1.4. McCullough et al. (2022)

McCullough et al. examined consumption of ASBs and all-cancer, obesity-related cancer (esophageal, stomach, colorectal, liver, gallbladder, pancreatic, post-menopausal breast, uterus/endometrial, ovarian, kidney and multiple myeloma), and site-specific cancer mortality in 934,777 participants enrolled in the Cancer Prevention Study-II (CPS-II) prospective cohort study [11]. Participants were asked at baseline (in 1982), "How many cups, glasses, or drinks of these beverages do you usually drink a day, and for how many years?" "Diet soda or diet iced teas" were considered ASBs. The authors also considered tabletop NSS packet intake, providing a more complete evaluation of exposure. Cancer outcomes were identified through inquiries by volunteers and were verified by death certificates and the National Death Index through 2016. This 34-year follow up period and the large size of the cohort are major strengths of this study, as is the adjustment for several key confounders in the analyses.

However, the exposure assessment in McCullough et al. was based on a single measurement [11], assessed 1 year prior to the regulatory approval of aspartame in carbonated beverages in the US. The authors provide no evidence that the patterns of consumption assessed prior to the approval of aspartame in this cohort would have remained following the approval and in the years and decades after. It has been demonstrated that consumption patterns of NSSs, particularly in US populations, have not remained constant over time [19].

Regardless, consumption of ASBs was not associated with liver cancer in the total population at any level of exposure [11]. The only statistically significant finding is a positive trend in non-smoking men with increasing ASB consumption ($p_{trend} = 0.040$), but this trend is no longer significant when the analysis is adjusted for BMI at baseline ($p_{trend} = 0.335$), and no associations were statistically significant in any individual exposure category in either case (i.e., < 1 drink, 1 drink, or > 1 drink per day). Further, the authors noted that they could not control for early adulthood BMI or diabetes diagnosis after baseline, which could have resulted in residual confounding and which could explain the trend observed in men who never smoked, as both are risk factors for liver cancer. It is also unclear whether ascertainment of deaths occurring before 1988 was complete, as they were identified by personal inquiries through volunteers. The authors themselves noted "measurement error was likely present" and "causality cannot be inferred."

1.5. 2023 JECFA review

JECFA concluded that evidence for aspartame carcinogenicity is "not convincing" and [6]:

> Statistically significant increases were reported for some cancers, such as hepatocellular, breast and hematological (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.

The liver cancer studies were discussed earlier. Schernhammer et al. [20] is the only cohort study of which we are aware that evaluated hematological cancers and reported a statistically significant increased association. This study was given "little weight" by the European Food Safety Authority [21], which stated there was no clear relationship between aspartame and blood cancer because of the small relative risks observed and major differences in results across men and women. Debras et al. [22], which was published after the previous WHO review [5], is the only study of which we are aware that has reported an increased risk of breast cancer associated with ASB consumption, and is discussed in more detail below and summarized in Table 1.

1.6. Debras et al. (2022)

Debras et al. [22] investigated artificial sweetener consumption and total cancer and obesity-related cancer risk between 2009 and 2021 in 102,865 participants at least 18 years of age enrolled in the NutriNet-Santé cohort in France. Participants were asked for information on dietary intakes over the previous 24-h three times in a 2-week period, every 6 months via an online questionnaire. The intakes reported during their first 2 years in the study were averaged to determine baseline intakes. Even though participants could have completed up to 15 24-h dietary records in the first 2 years of the study, nearly half of those classified as non-consumers and more than one third of consumers completed only two or three records.

The reported food products were linked to three databases to estimate aspartame and general NSS consumption in the full diet (food, beverage, and tabletop packets). Potential reformulations of products were also considered. A strength of the exposure assessment in this study is that, in addition to multiple assessments over time, consumption of aspartame in addition to the non-specific aggregate of nine types of ASBs was captured and evaluated. Data were validated with in-person interviews by trained dieticians. Participants were divided into non-consumers, low-consumers, or high-consumers of aspartame.

When comparing high consumers to non-consumers, the authors reported aspartame consumption was associated with increases in risk of total cancer (HR = 1.15, 95% CI: 1.03–1.28) and obesity-related cancer (HR 1.15, 95% CI 1.01–1.32) [22]. These reported associations were observed among participants who filled out a minimum of two (of a maximum of 15) 24-h dietary records within the first 2 years. These associations were no longer statistically significant when the study population was restricted to participants with at least four 24-h dietary records during the first 2 years (total cancer HR = 1.06, 95% CI: 0.94–1.19; obesity-related cancers HR = 1.05, 95% CI: 0.91–1.22; breast cancer HR = 1.07, 95% CI: 0.87–1.32; prostate cancer HR = 1.19, 95% CI: 0.84–1.69). Site-specific analyses controlled for important potential confounders, but it is unlikely that all important confounders were controlled for in the aggregated total cancer or obesity-related cancer analyses. The fact that associations were attenuated after individuals with less data were excluded adds to the uncertainty regarding the reported associations.

When pre- and postmenopausal breast cancer cases were combined, a small increased risk of breast cancer was reported (HR = 1.22, 95% CI: 1.01–1.48) [22]. However, when stratified by menopausal status, the associations were no longer statistically significant (i.e., pre-menopausal: HR = 1.07, 95% CI: 0.79–1.46; post-menopausal: HR = 1.24, 95% CI: 0.98–1.57). Further, as noted above, a positive association between aspartame and breast cancer was not observed in other prospective cohort studies, including those that accounted for frequency and changes in consumption over time (e.g., Romanos-Nanclares et al. [23], Malik et al. [24]).

Debras et al. noted selection bias, residual confounding, and reverse causality as possible explanations for any reported associations [22], and that "causal links cannot be established by this unique study." They also stated that their findings "need to be replicated in other large-scale cohorts, and underlying mechanisms clarified by experimental studies." Others have noted further weaknesses [13,25]: This cohort was recruited online and was mostly women, with a short duration of follow-up (median: 7.8 years), which may have varied between aspartame categories; those who volunteered to participate differed from the broader population with respect to socioeconomic status and lifestyle factors; and, finally, it appears that only baseline data (24-h dietary recall records averaged over the first 2 years after enrollment) were used to assess exposure, and this may not have accurately reflected aspartame

consumption over those 2 years, given the low proportion of completed surveys, and also may not have reflected exposure during the remainder of follow up [22,25].

2. Conclusion

While decades of research have indicated that aspartame is not a human cancer hazard, IARC classified it as a Group 2B possible human carcinogen [6,8]. This was based on three human studies that reported a few positive findings for liver cancer, and that also have a high likelihood of exposure misclassification and similar weaknesses to other studies IARC concluded were inadequate. More importantly, the positive findings are not consistent within or across these three studies (e.g., a statistically significant finding that loses significance when adjusted for BMI or when assessed for longer follow-up periods is not convincing evidence of a causal association).

IARC [8] paradoxically concluded that human evidence for aspartame and liver cancer is "high quality" but also "limited" because chance, bias, and confounding cannot be ruled out with confidence in the relevant epidemiology literature. It is not clear how IARC can conclude these studies can be both high quality and have these weaknesses at the same time. This IARC conclusion is also inconsistent with those of WHO [5] and JECFA [6,7]. Both WHO [5] and JECFA [6,7] concluded that this degree of uncertainty means that the evidence is uninformative, and does not support human carcinogenicity, even in a limited way. Indeed, if chance, bias, and confounding cannot be ruled out with confidence, then the evidence should be considered inadequate to address causality, as the word "limited" implies that the evidence may support causation, as opposed to being uninformative due to weaknesses in the studies themselves.

The results of the IARC and JECFA assessments illustrate the conflicting and confusing messaging around these evaluations, particularly when the strength of the evidence is tenuous, at best. One way that IARC could provide clarity in its carcinogenicity classifications would be to reclassify agents that are currently Group 2B as Group 3 if the 2B classification is based on a positive association in human studies but chance, bias, and confounding cannot be reasonably ruled out, and if there is not sufficient animal evidence or strong mechanistic evidence. Ultimately, the interpretation of a Group 2B classification based on limited human evidence and a Group 3 classification is intended to be similar, i.e., the evidence is not sufficient to judge whether causation is likely [12,26]. However, the designation of an agent as a Group 2B possible carcinogen makes it appear to scientists and non-scientists alike that the evidence is pointing in the direction of causality. Also, in this case, it implies that the IARC conclusion conflicts with that of WHO [5] and JECFA [6,7], both of which state that the evidence is unconvincing or inadequate to make a judgment. This has led to unnecessary confusion, which could have easily been avoided with the classification most consistent with the existing data: Group 3, "not classifiable as to its carcinogenicity."

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Declaration of Competing Interest

MMJ is an employee of ABA. She serves as Chief Science and Regulatory Officer in that role. JEG and DNB are employees of Gradient, a private environmental consulting firm. Work on this paper was conducted during the authors' normal course of employment. The authors had sole responsibility for the writing and content of this paper, which represents the professional opinions of the authors and not necessarily those of ABA.

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