

# ASPARTAME, METHYLEUGENOL, AND ISOEUGENOL

VOLUME 134

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ON THE IDENTIFICATION  
OF CARCINOGENIC HAZARDS  
TO HUMANS

**Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame**

| Reference and outcome                                                | What was the study design?                                      | What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)                                                                                                                                                                                                                                        | What was the exposure context?<br>Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)<br>What was the agent under investigation?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Was estimate of exposure qualitative, semiquantitative, or quantitative?                                              | Which exposure sources were assessed?                                                                                                                                                                                                                                                                                         | What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)?<br>(specify units)                                                         | What was the timing of exposure relative to the outcome?                                      | Which other potential carcinogens, confounders, or effect modifiers were assessed?                                                                                                                                          | Was there potential for differential exposure misclassification?<br>Was there potential for non-differential exposure misclassification?<br>(Likely/unlikely)                                                                                                           |
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| Andreatta et al. (2008)<br>Urinary tract tumours                     | Case-control                                                    | Interview by a nutritionist<br><br>Habitual use of AS in the past 5 yr: ever consumption (yes/no), brand name, duration of consumption<br><br>Classification of participants in 3 categories: non-AS consumers, AS short-term consumers (1–9 years), and AS long-term consumers (10 or more years)                                                              | What: artificial sweeteners (two subgroups: saccharine/cyclamate and aspartame/acesulfame-K used for description but not for analyses)<br><br>Where: Argentina<br><br>When: 1999 to 2006<br><br>Context: 14% of the population regularly use AS to sweeten drinks and foods, saccharin and cyclamate are the most frequently consumed, aspartame and acesulfame-K used by a smaller percentage                                                                                                                                                                                                                                                                                                             | Qualitative (ever use)<br><br>Quantitative (duration of use)                                                          | Use of AS in infusions (tea, coffee, mate)<br><br>No data on other sources (soft drinks, dietetic foods)                                                                                                                                                                                                                      | Ever use and duration of use (years)                                                                                                                                                                     | Usual diet assessed for the 5 yr before diagnosis or hospitalization                          | Potential co-exposure measured and considered in analyses: smoking, BMI, tobacco use, mate/infusion drinking (“hot beverage”)                                                                                               | Differential likely: case-control study; retrospective assessment of AS consumption<br><br>Non-differential likely: memory bias; only one source of AS considered; no specific assessment of aspartame                                                                  |
| Bao et al. (2008)<br>Pancreatic cancer                               | Cohort (NIH-AARP Diet and Health Study)                         | Self-administered baseline FFQ (124 items, past 12 months) validated against two 24-hour recalls<br><br>Consumption of 3 types of soft drinks assessed through 10 frequencies (“never” to “6+ times per day”), 3 portion size ranges and the frequency of sugar-free (diet) or regular-calorie version of these beverages (usually, or more than half the time) | What: diet soft drinks<br><br>When: diet data collected in 1995–1996, follow-up until 2003<br><br>Where: USA<br><br>Context:<br><br>*limited history of use of aspartame before study baseline: aspartame use started in 1981 for dry foods (incl. tabletop sweetener), in 1983 for carbonated beverages, in 1993 for other beverages, baked goods, and confections, and in 1996 for all foods and beverages<br><br>*soft drinks > 70% of aspartame sales in the USA in early 2000s<br><br>*aspartame as main artificial sweetener in beverages in the 1980s and 1990s (before 1983: only saccharin, after 1983: mainly aspartame in soft drinks, 1998–2002: acesulfame-K, sucralose and neotame approved) | Quantitative                                                                                                          | 3 potentially aspartame-containing beverages: sugar-free or “diet” version of soda, fruit drinks, and iced tea<br><br>No data on other potential sources: “diet” version of foods, such as yogurt, gelatin/pudding, ice cream and frozen desserts, and hot chocolate (50 mg or more aspartame per serving in the early 2000s) | Average daily consumption<br><br>Quintiles or never drinkers and quintiles in drinkers                                                                                                                   | Usual diet assessed in 1995–1996, follow-up until 2003                                        | Potential co-exposure measured and considered in analyses: BMI, alcohol, smoking, physical activity, energy-adjusted intakes of total fat, saturated fat, red meat and folate, multivitamins, regular soft drinks, diabetes | Differential unlikely: cohort study; diet soft drink consumption assessed before cancer diagnosis<br><br>Non-differential likely: only one potential source of aspartame considered (diet soft drinks), uncertainty regarding the content of the beverages in aspartame |
| Bassett et al. (2020)<br>Cancers not related to obesity              | Prospective cohort study (Melbourne Collaborative Cohort Study) | Self-administered 121-item FFQ with separate questions on frequency of consumption in the past year of diet (artificially sweetened) soft drinks                                                                                                                                                                                                                | What: Artificially sweetened soft drink<br><br>Where: Australia<br><br>When: Baseline data collected 1990–1994                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Semiquantitative                                                                                                      | Artificially sweetened soft drink                                                                                                                                                                                                                                                                                             | Frequency of consumption (Never or < 1/month, 1–3/month, 1–6/week, 1/day, > 1/day)                                                                                                                       | Baseline data collected 1990–1994 on consumption in previous 12 months with follow-up to 2015 | Other co-exposures: Mediterranean diet score, BMI, Waist, smoking, leisure time physical activity, alcoholic beverages                                                                                                      | Differential unlikely: cohort study with assessment before diagnosis<br><br>Non-differential likely: only ASB as a proxy measure                                                                                                                                        |
| Bosetti et al. (2009)<br>Stomach, pancreatic and endometrial cancers | Case-control                                                    | Reproducible and valid FFQ (78 items, past 2 yr before diagnosis or hospital admission)<br><br>Weekly consumption of sachets or tablets of saccharin and other sweeteners                                                                                                                                                                                       | What: sweeteners (saccharin and ‘other sweeteners’, described as “mainly aspartame” by the authors)<br><br>Where: Italy<br><br>When: 1997–2007 (stomach), 1991–2007 (pancreas), 1992–2006 (endometrium)<br><br>Context: recent introduction of diet soft drinks and low frequency of consumption in middle age and elderly in this population (unlikely to have a major contribution to cancer development)                                                                                                                                                                                                                                                                                                | Qualitative (low-calorie sweeteners, saccharin and other sweeteners)<br><br>Semiquantitative (low-calorie sweeteners) | -sachets or tablets of sweeteners<br><br>Other sources of sweeteners (ASB) not considered but not widespread at the time of the study                                                                                                                                                                                         | Average daily consumption in sachets or tablets/day<br><br>Ever users/non-users of low-calorie sweeteners, saccharin and other sweeteners; > 2 vs 0 sachets or tablets per day of low-calorie sweeteners | Usual diet assessed for the 2 yr before diagnosis (cases) or hospital admission (controls)    | Potential co-exposure measured and considered in analyses: BMI, smoking, alcohol, diabetes, hot beverages (incl. coffee, decaffeinated coffee, tea)                                                                         | Differential likely: case-control study; retrospective assessment of sweeteners consumption<br><br>Non-differential likely: memory bias; only one source of aspartame considered; no specific assessment of aspartame (‘other sweeteners’ although mainly aspartame)    |

**Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame**

| Reference and outcome                                                                                                                                                                                          | What was the study design?                       | What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)                                                                                                                                                                                                                                                                               | What was the exposure context?<br>Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)<br>What was the agent under investigation?                                                                                              | Was estimate of exposure qualitative, semiquantitative, or quantitative? | Which exposure sources were assessed?                                                                                                                                                       | What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)?<br>(specify units)                    | What was the timing of exposure relative to the outcome?                                                                                                                                         | Which other potential carcinogens, confounders, or effect modifiers were assessed?                                                                                                                                                         | Was there potential for differential exposure misclassification?<br>Was there potential for non-differential exposure misclassification?<br>(Likely/unlikely)                              |
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| Cabaniols et al. (2011)<br>Brain cancer                                                                                                                                                                        | Case-control study                               | Self-administered questionnaire on gender, date of birth, socioeconomic and marital status, stress, hobbies, diet and place of residence; question on aspartame consumption frequency for the past 5 yr. Person-to-person interview for medical questionnaire and missing data from self-administered questionnaire                                                                                    | What: Aspartame consumption frequency<br>Where: France<br>When: Data collected 2005                                                                                                                                                                                                            | Semiquantitative                                                         | Aspartame                                                                                                                                                                                   | Non-consumers (< 1 per week) and regular consumers (≥ 1 per week)                                                                                                   | Previous 5 yr before diagnosis                                                                                                                                                                   | Other co-exposures: BMI, other dietary habits (vegetables, fruit);<br><br>Two daily meals; skipping meals; vitamin supplement; physical activity, smoking, alcohol, cannabis                                                               | Differential likely: case-control study; retrospective assessment<br><br>Non-differential likely: only frequency collected, measurement validity of questions unclear                      |
| Chan et al. (2009)<br>Pancreatic cancer                                                                                                                                                                        | Population-based case-control study              | 131-item food validated questionnaire via in-person interviews, previous 1 months                                                                                                                                                                                                                                                                                                                      | What: total sugar-free carbonated beverages/day<br>Where: California, USA<br>When: data collected 1995 and 1999                                                                                                                                                                                | Semiquantitative                                                         | Total sugar-free carbonated beverages/day (low-calorie colas, low-calorie caffeine-free colas, and other low-calorie carbonated beverages such as Diet 7-up, Fresca, diet ginger ale, etc.) | Total sugar-free carbonated beverages/day (0, < 1, ≥ 1)<br><br>By type of carbonated beverage: < 1/month, 1–3/month, 1–6/week, ≥ 1/day                              | Previous 12 months before diagnosis                                                                                                                                                              | Other co-exposures: BMI, cigarette smoking, physical activity, other food groups (red meat, white meat, dairy, vegetable and fruit, eggs, fish, whole grain, and refined grain), history of diabetes, sugar-sweetened beverages and sweets | Differential likely: case-control study; retrospective assessment<br><br>Non-differential likely: only ASB as a proxy measure                                                              |
| Chazelas et al. (2019)<br>All cancers combined, breast, colorectal, prostate                                                                                                                                   | Prospective cohort study (Nutrinet-Santé cohort) | Participants are asked every 6 months to complete a series of 3 validated web-based 24 h dietary records randomly assigned over a two-week period (2 weekdays, 1 weekend day)<br><br>At least 2 24-hour dietary records during the first 2 yr of follow-up considered in analyses (mean ± SD, 5.6 ± 3.0)                                                                                               | What: Artificially sweetened soft drink<br>Where: France<br>When: Data collected from 2009–2017, follow-up to Jan 2018, median follow-up time 5.1 yr                                                                                                                                           | Quantitative                                                             | 12 ASB items all beverages containing non-nutritive sweeteners, such as diet soft drinks, sugar-free syrups, and diet milk-based beverages                                                  | ASBs (mL/d); sex-specific cut-offs for quartiles of artificially sweetened beverages intake were 2.7, 4.7, and 7.9 mL/d in men and 4.6, 7.7, and 11.6 mL/d in women | Data collected from 2009–2017, follow-up to Jan 2018, median follow-up time, 5.1 yr                                                                                                              | Other co-exposures: sugar intake from other dietary sources (all sources except sugary drinks), alcohol, sodium, fat and fruit and vegetable intakes, BMI, physical activity, smoking status                                               | Differential unlikely: cohort study with assessment before diagnosis<br><br>Non-differential likely: only ASB as a proxy measure                                                           |
| Davis et al. (2023)<br>Pancreatic cancer and mortality                                                                                                                                                         | Case-control                                     | 46-item FFQ regarding general dietary habits (incl. daily consumption of ASB) in the few years before diagnosis                                                                                                                                                                                                                                                                                        | What: ASB<br>When: retrospective assessment of diet before diagnosis between 1982 and 1998<br>Where: USA (Buffalo, NY)<br>Hospital-based                                                                                                                                                       | Semiquantitative                                                         | Diet cola                                                                                                                                                                                   | 3 categories: never, occasional (< 1 drink/day), and habitual (1+ drinks/day) consumers                                                                             | Retrospective assessment of exposure in the few years before diagnosis between 1982 and 1998                                                                                                     | Potential co-exposure measured and considered in analyses: smoking status, BMI, vegetable intake, processed meat intake, family history of pancreatic cancer, radiation status                                                             | Differential likely: retrospective assessment; case-control study<br><br>Non-differential likely: no details on aspartame; only ASB (diet cola) consumption as potential source            |
| Debras et al. (2022)<br>All cancers combined, breast, prostate, all obesity-related cancers combined (colorectal, stomach, liver, mouth, pharynx, larynx, oesophageal, breast, ovarian, endometrial, prostate) | Prospective cohort study (Nutrinet-Santé cohort) | Participants are asked every 6 months to complete a series of 3 validated web-based 24 h dietary records randomly assigned over a 2-wk period (2 weekdays, 1 weekend day)<br><br>At least 2 24-hour dietary records during the first 2 yr of follow-up considered in analyses (mean (SD) of 5.6 (3.0))<br><br>Sensitivity analyses conducted using all 24 h dietary records available during follow-up | What: aspartame<br>When: baseline data collected 2009–2021, median follow-up time = 7.8 yr.<br>Context: date of consumption of each food or beverage declared by each participant was used to match the product to the closest composition data, thus accounting for potential reformulations. | Quantitative                                                             | Aspartame                                                                                                                                                                                   | Aspartame mg/day                                                                                                                                                    | Baseline dietary intakes were evaluated by averaging all 24-hour dietary records provided during the first 2 yr of follow-up.<br><br>Sensitivity analysis with time-dependent aspartame exposure | Other co-exposures: physical activity, smoking, BMI; alcohol, other dietary exposures (sodium, saturated fatty acids, fibre, sugar, fruit and vegetables, whole-grain foods, and dairy products)                                           | Differential unlikely: cohort study with assessment before diagnosis<br><br>Non-differential unlikely: measurement of aspartame with food composition data adjusted with changes over time |

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| Ewertz and Gill (1990)<br><br>Breast                                                                                                   | Case-control study         | Self-administered, semiquantitative food frequency questionnaire with additional questions on consumption of tea, coffee, sugar, and artificial sweeteners                                                                                                                                                                                                                                                        | What: usage of Sweeteners in coffee and tea<br>Where: Denmark.<br>When: 1 March 1983 to 29 February 1984                                                                                                                                                                                                     | Qualitative                                                                                                           | Usage of sweeteners in coffee and tea                                                                                                                                                                      | Usage of sweeteners in coffee and tea (yes/no)                                                                                                                                                                                                      | Previous 12 months before diagnosis                                                                                            |                                                                                                                                                                  | Differential likely: case-control study; retrospective assessment<br><br>Non-differential likely: only sweeteners in tea and coffee as a proxy measure                                                                                                                                                                                                                   |
| Fulgoni and Drewnowski (2022)<br><br>Cancer mortality                                                                                  | Cohort (NHANES)            | One or two 24 h recalls by a trained interviewer<br><br>Identification of products containing low-calorie sweeteners (no separation by brand name: e.g. Aspartame, sucralose, saccharin)<br><br>Less than 2% ( <i>n</i> = 165) of food items were classified as containing low-calorie sweeteners<br><br>In NHANES 1988–1994: specific questions regarding aspartame or saccharin (sodas, added sweeteners, etc.) | What: low-calorie sweeteners<br>When: cross-sectional surveillance studies in 1988–1994 and 1999–2018<br>Where: USA<br><br>Context: low-calorie sweeteners consumed by 41.4% of US adults in NHANES cycles 2009–2012                                                                                         | Quantitative                                                                                                          | Diet beverages, including diet sodas and other diet beverages (fruit-based and other), tabletop sweeteners, and low-calorie sugar-free foods such as yogurts, ice cream, grain-based desserts, and candies | Non-consumers and tertiles of gram weight of low-calorie sweetener beverages and foods in consumers<br><br>Tertiles of aspartame only in NHANES 1988–1994; tertiles of low-calorie sweetener products in NHANES 1988–1994, 1999–2018, and 1988–2018 | Aspartame exposure assessed in 1988–1994; low-calorie sweetener assessed in 1988–1994 or 1999–2018<br><br>Follow-up until 2019 | Potential co-exposure measured and considered in analyses: current smoking status, alcohol consumption, physical activity, BMI                                   | Differential unlikely: prospective design<br><br>Non-differential likely: only one or maximum 2 dietary recalls; no specific assessment of aspartame in cycles 1999–2018                                                                                                                                                                                                 |
| Gallus et al. (2007)<br><br>Cancers of the oral cavity and pharynx, oesophagus, colon, rectum, larynx, breast, ovary, prostate, kidney | Case-control               | Reproducible and valid FFQ (78 items, past 2 yr before diagnosis or hospital admission)<br><br>Weekly consumption of sachets or tablets of saccharin and other sweeteners                                                                                                                                                                                                                                         | What: sweeteners (saccharin and others including mainly aspartame)<br>Where: Italy<br>When: 1991 to 2004<br><br>Context: recent introduction of diet soft drinks and low frequency of consumption in middle age and elderly in this population (unlikely to have a major contribution to cancer development) | Qualitative (low-calorie sweeteners, saccharin and other sweeteners)<br><br>Semiquantitative (low-calorie sweeteners) | Sachets or tablets of sweeteners<br><br>No data on other sources (soft drinks, dietetic foods)                                                                                                             | Average daily consumption in sachets or tablets/day<br><br>Ever users/non-users of low-calorie sweeteners, saccharin and other sweeteners; > 2 vs 0 sachets or tablets per day of low-calorie sweeteners                                            | Usual diet assessed for the 2 yr before diagnosis (cases) or hospital admission (controls)                                     | Potential co-exposure measured and considered in analyses: alcohol, tobacco smoking, BMI, hot beverages, sugar                                                   | Differential likely: case-control study; retrospective assessment of sweeteners consumption<br><br>Non-differential likely: memory bias; only one source of sweeteners considered; no specific assessment of aspartame ('other sweeteners' although mainly aspartame)                                                                                                    |
| Gurney et al. (1997)<br><br>Childhood brain tumours                                                                                    | Case-control               | In-person interview of biological mothers on:<br><br>Children's consumption of aspartame before the date of diagnosis (cases) or comparable reference date (controls)<br><br>Mother's consumption of aspartame during pregnancy and breastfeeding                                                                                                                                                                 | What: aspartame<br>When: cases and controls born in 1981 or later; cases diagnosed with a primary brain tumour between 1984 and 1991<br>Where: USA<br><br>Exposure assessed from the introduction of aspartame on the US market, but contains 3 yr in which aspartame was not used in beverages (1981–1984)  | Semiquantitative                                                                                                      | Any food, chewing gum, or diet drink containing aspartame; Nutrasweet                                                                                                                                      | Children: age at first consumption, time period of consumption, frequency of consumption<br><br>Mothers: trimesters of consumption, time period of consumption, frequency of consumption during pregnancy or while breastfeeding                    | Exposure to aspartame before cancer diagnosis (between 1984 and 1991) of children born or in utero in 1981 and later           | Potential co-exposure measured and considered in analyses: maternal vitamin use, cured meat consumption, passive smoke exposure, X-ray exposure                  | Differential likely: case-control study; retrospective assessment: memory bias for the assessment of aspartame consumption (children and mother during their pregnancy) several years in the past<br><br>Non-differential likely: only frequency and period of consumption (no dose); unclear and unspecific sources of aspartame; mothers assess children's consumption |
| Heath et al. (2021)<br><br>Renal cell carcinoma incidence and mortality                                                                | Cohort (EPIC)              | Usual diet over the previous 12 months<br><br>Country-specific instruments developed and validated within the various source populations and including hundreds of                                                                                                                                                                                                                                                | What: artificially sweetened soft drinks<br>When: ASB assessed at inclusion between 1992 and 2000<br><br>Where: western European countries (Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, United                                                                                              | Quantitative                                                                                                          | Carbonated/ soft/ isotonic drinks, and diluted syrups: "low-calorie or diet fizzy soft drinks", "fizzy soft drinks, e.g. cola, lemonade", and "fruit squash or cordial"                                    | Mean daily intakes over the past 12 months<br><br>Risk estimates per 100 g/day                                                                                                                                                                      | Diet questionnaires covering the past year between 1991 and 2000<br><br>-mean follow-up of 15 yr for incidence of              | Potential co-exposure measured and considered in analyses: smoking, alcohol, physical activity, juice intake, total soft drink, BMI, fruit and vegetable intake, | Differential unlikely: cohort study; exposure assessed before cancer diagnosis<br><br>Non-differential likely: no details on aspartame; only ASB as potential sources of                                                                                                                                                                                                 |

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|                                                        |                                                           | country- and region-specific foods. These extensive self-administered quantitative dietary questionnaires collected usual portions and frequency of consumption of up to 260 food items food and drinks during different seasons of the year.<br><br>Soft drink consumption: number of glasses (typical glass sizes in each centre, ≈ 250 mL) per month, week, or day | Kingdom); data on artificially sweetened soft drinks not available in Spain, Italy (Florence, Turin, Ragusa, Varese) and Sweden (Umea)<br><br>-context: multiple European countries and associated context of consumption, no information on historical exposure |                                                                          | Total soft drinks: sugar-sweetened/artificially sweetened                                 |                                                                                                                                                                                                                                                                                                                                                             | renal cell carcinoma and 16 yr for mortality                                                  | diabetes, sugar-sweetened soft drinks                                                                                                                                                                                                                                                                                                                                                                                                  | aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline in a context of low consumption of AS soft drinks; potential variations of the content of AS soft drinks in aspartame; measurement errors                                                                                                                                                                                                        |
| Hodge et al. (2018)<br><br>Obesity-related cancers     | Prospective cohort study (Melbourne Collaborative cohort) | Self-administered 121-item FFQ with separate questions on frequency of consumption in the past year of diet (artificially sweetened) soft drinks                                                                                                                                                                                                                      | What: artificially sweetened soft drink<br><br>Where: Australia<br><br>When: Baseline data collected 1990–1994                                                                                                                                                   | Semiquantitative                                                         | Artificially sweetened soft drink                                                         | Frequency of consumption (Never or < 1/month, 1–3/month, 1–6/week, 1/day, > 1/day)                                                                                                                                                                                                                                                                          | Baseline data collected 1990–1994 on consumption in previous 12 months with follow-up to 2015 | Other co-exposures: Mediterranean diet score, BMI, waist circumference, smoking, leisure time physical activity, alcoholic beverages                                                                                                                                                                                                                                                                                                   | Differential unlikely: cohort study with assessment before diagnosis<br><br>Non-differential likely: only ASB as a proxy measure                                                                                                                                                                                                                                                                                                                            |
| Hur et al. (2021)<br><br>Early-onset colorectal cancer | Cohort (NHSII)                                            | Validated, semiquantitative FFQ (130 items, past 12 months) every 4 yr since 1991<br><br>Dietary intake in adolescence assessed in 1998 through a high-school (HS)-FFQ (124 items typically consumed between 1960 and 1982)                                                                                                                                           | What: artificially sweetened beverages<br><br>When: adult diet assessed every 4 yr since 1991; adolescent diet (between 1960 and 1982) assessed in 1998<br><br>Where: USA<br><br>Context: no aspartame in soft drinks before 1983                                | Semiquantitative                                                         | Low-calorie carbonated beverages                                                          | Cumulative average of beverage intake collected across all available FFQs from the study baseline up to each questionnaire cycle<br><br>ASBs categorized as < 1 serving/week, 1 serving/week to < 1 serving/day, 1 to < 2 servings/day, ≥ 2 servings/day) + per each serving/day; one standard serving size in adults: 12 ounces (oz), in adolescence: 8 oz | FFQ in 1991 and then every 4 yr, follow-up until 2015                                         | Potential co-exposure measured and considered in analyses (adulthood and adolescence): BMI, menopausal hormone, smoking, physical activity, aspirin or NSAIDs, multivitamins, alcohol, red and processed meat, dietary fibre, total folate and total calcium, diet quality (AHEI-2010), sugar-sweetened beverages, diabetes (low proportion)<br><br>Reduction in milk consumption concomitant to an increase in soft drink consumption | Differential unlikely: cohort study; exposure assessed before cancer diagnosis<br><br>Non-differential likely: no details on aspartame; only ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of AS soft drinks in aspartame; measurement errors                                                                                                                 |
| Inoue-Choi et al. (2013)<br><br>Endometrial cancer     | Cohort (Iowa Women’s Health Study (IWHs))                 | Harvard semiquantitative FFQ at study baseline (127 items, past 12 months)<br><br>Standard serving size<br><br>Follow-up survey with a FFQ in 2004: correlation coefficient of 0.23 for SSBs                                                                                                                                                                          | What: sugar-free beverages<br><br>When: FFQ in 1986 (baseline)<br><br>Where: USA                                                                                                                                                                                 | Quantitative                                                             | Low-calorie caffeinated and caffeine-free cola and other low-calorie carbonated beverages | Quintiles of energy-adjusted intake of sugar-free beverages (servings/wk)                                                                                                                                                                                                                                                                                   | Diet assessed in 1986, follow-up until 2010                                                   | Potential co-exposure measured and considered in analyses: smoking, physical activity, alcohol, estrogen, diabetes, coffee, BMI                                                                                                                                                                                                                                                                                                        | Differential unlikely: cohort study; exposure assessed before cancer diagnosis<br><br>Non-differential likely: no details on aspartame; only ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of AS soft drinks in aspartame over time; only one dietary assessment at baseline: possible variations of AS soft drinks consumption over time; measurement errors |

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| Reference and outcome                                                     | What was the study design?                                                                                                                   | What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)                                                                                                                                                                                                                        | What was the exposure context?<br>Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)<br>What was the agent under investigation?                                                                          | Was estimate of exposure qualitative, semiquantitative, or quantitative? | Which exposure sources were assessed?                                                                                                                                                         | What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)?<br>(specify units)                                                                                                                                                                 | What was the timing of exposure relative to the outcome?                                             | Which other potential carcinogens, confounders, or effect modifiers were assessed?                                                                                                                                                                                                                                                                                                | Was there potential for differential exposure misclassification?<br>Was there potential for non-differential exposure misclassification?<br>(Likely/unlikely)                                                                                                                                                                                                                                                                         |
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| Joh et al. (2021)<br>Colorectal cancer precursors (polyp, adenoma)        | Cohort (NHSII)                                                                                                                               | Adolescent diet assessed in 1998 using a self-administered HS-FFQ (124-item, food items commonly consumed between 1960 and 1982 when participants were in high school (13–18 yr old))<br><br>Adult diet assessed every 4 yr since 1991 using a validated FFQ (131 items)<br><br>Standard serving sizes: 1 glass, a bottle, or a can (12 ounces) | What: ASB<br><br>When: adolescence between 1960 and 1982<br><br>Where: USA<br><br>Context: no aspartame in soft drinks before 1983                                                                                                                                         | Semiquantitative                                                         | Carbonated and non-carbonated low-calorie or diet beverages                                                                                                                                   | Estimates for adolescent ASB intake per 1 serving/d increase and from 4 categories: < 1 serving/week, 1–6 servings/week, 1 serving/day, and ≥ 2 servings/day<br><br>Adult diet: cumulative updated intake (average of the repeated measures from all available FFQs up to 2 yr before the most recent endoscopy) | Adolescence intake between 1960 and 1982, follow-up between 1998 and 2015                            | Potential co-exposure measured and considered in analyses: menopausal hormone, aspirin diabetes, BMI, smoking, alcohol, physical activity, adolescent and adult dietary intakes of total calcium, vitamin D, total folate, total fibre, fruits, vegetables, and dairy, adult intake of total red meat, western dietary pattern score during adolescence, adult intake of ASB, IBD | Differential unlikely: cohort study; exposure assessed before diagnosis<br><br>Non-differential likely: recall bias from adult recall of adolescent diet; no details on aspartame; only ASB as potential sources of aspartame; ASB in the time period of adolescence likely contained no aspartame; measurement errors; recalled adolescent diet only weakly correlated with adult diet                                               |
| Jones et al. (2022)<br>Liver and biliary duct cancer                      | Pooled analysis of 2 cohort studies: NIH-AARP Diet and Health Study, and Prostate Lung, Colorectal and Ovarian cancer screening trial (PLCO) | NIH-AARP: FFQ at baseline in 1995–1996<br><br>PLCO: diet history questionnaire (DHQ) in 1998<br><br>Frequency of consumption of ASB (from no consumption to 6+ times per day)<br><br>No information on the volume consumed                                                                                                                      | What: ASB<br><br>When: diet assessed in 1995–1996 (NIH-AARP) and 1998 (PLCO)<br><br>Where: USA                                                                                                                                                                             | Quantitative                                                             | Soda, fruit punches                                                                                                                                                                           | Mean daily frequency, estimates for an increase of one consumption frequency per day                                                                                                                                                                                                                             | Diet assessed in 1995–1996 (NIH-AARP) or 1998 (PLCO), follow-up until 2011 (NIH-AARP) or 2017 (PLCO) | Potential co-exposure measured and considered in analyses: BMI, smoking, alcohol, diabetes                                                                                                                                                                                                                                                                                        | Differential unlikely: cohort study; exposure assessed before cancer diagnosis<br><br>Non-differential likely: no details on aspartame; only ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of ASB in aspartame over time; only one dietary assessment at baseline: possible variations of ASB consumption over time; measurement errors |
| Kobeissi et al. (2013)<br>Urinary bladder cancer                          | Case–control                                                                                                                                 | -face to-face interview questionnaires<br><br>-“artificial sweetener consumption”                                                                                                                                                                                                                                                               | What: artificial sweeteners<br><br>When: between 2002 and 2008<br><br>Where: Lebanon                                                                                                                                                                                       | Qualitative                                                              | Artificial sweeteners                                                                                                                                                                         | Frequency of artificial sweetener intake: never, rarely, frequently, always                                                                                                                                                                                                                                      | Before diagnosis                                                                                     | Potential co-exposure measured and considered in analyses: smoking, UTD (infections and stones), hair dyes, occupational chemical exposure, passive smoking                                                                                                                                                                                                                       | Differential likely: retrospective assessment; not possible to mask the interviewers on the subject’s status<br><br>Non-differential likely: no details on aspartame; unclear source “artificial sweeteners”; only broad frequency of use; measurement errors                                                                                                                                                                         |
| Larsson et al. (2016)<br>Cancers of the biliary tract and the gallbladder | Cohort (Swedish Mammography Cohort (SMC) and Cohort of Swedish Men (COSM))                                                                   | Self-administered semiquantitative FFQ (96 items, past year)<br><br>Usual consumption of a standard glass (200 mL) of sweetened beverages<br><br>No distinction between sugar-sweetened and artificially sweetened (low-calorie) beverages                                                                                                      | What: sweetened beverages<br><br>When: FFQ in 1997<br><br>Where: Sweden<br><br>Context: low-calorie soft drinks and “juice” drinks accounted for 9.9% (men) to 19.2% (women) of total soft drink and “juice” drink consumption in 1997 (Swedish national consumption data) | Semiquantitative                                                         | Sweetened beverage (not including fruit juices, energy and sports drinks, or sweetened coffee, tea, or milk) without distinction between sugar-sweetened and artificially sweetened beverages | Mean daily intake<br><br>Non-consumers and quartiles of consumption among consumers (0.1–0.4, 0.5–1.9, and 2 servings/day); per 1 serving per day                                                                                                                                                                | FFQ in 1997, follow-up until 2012 (mean follow-up of 13.4 yr)                                        | Potential co-exposure measured and considered in analyses: smoking, BMI, protein, total fat, carbohydrates, fruit juice, coffee, tea, and milk, alcohol, physical activity, diabetes                                                                                                                                                                                              | Differential unlikely: cohort study; exposure assessed before cancer diagnosis<br><br>Non-differential likely: no distinction between sugar-sweetened and artificially sweetened beverages; no details on aspartame; only sugar-sweetened beverage as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame;                                                                                |

**Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame**

| Reference and outcome                                   | What was the study design?                          | What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)                                                                                                                                                                                                                                                                                                                                  | What was the exposure context?<br>Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)<br>What was the agent under investigation?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Was estimate of exposure qualitative, semiquantitative, or quantitative? | Which exposure sources were assessed?                                                                                                                                                                                                                                                                                                                                      | What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)?<br>(specify units)                                                                                                                                                                                                                                                                                                                                                                               | What was the timing of exposure relative to the outcome?                              | Which other potential carcinogens, confounders, or effect modifiers were assessed?                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Was there potential for differential exposure misclassification?<br>Was there potential for non-differential exposure misclassification?<br>(Likely/unlikely)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| Lim et al. (2006)<br>Haematopoietic cancers and gliomas | Prospective Cohort (NIH-AARP Diet and Health Study) | Self-administered baseline FFQ (124 items, past 12 months) validated against two 24-hour recalls<br><br>Consumption of 3 types of soft drinks assessed through 10 frequencies (“never” to “6+ times per day”), 3 portion size ranges and the frequency of sugar-free (diet) or regular-calorie version of these beverages (usually, or more than half the time)<br><br>Tabletop packet of aspartame added to cups of coffee and hot tea                   | What: aspartame<br><br>When: diet data collected in 1995–1996, follow-up until 2000<br><br>Where: USA<br><br>Context:<br>*limited history of use of aspartame before study baseline: aspartame use started in 1981 for dry foods (incl. tabletop sweetener), in 1983 for carbonated beverages, in 1993 for other beverages, baked goods, and confections, and in 1996 for all foods and beverages<br><br>*soft drinks > 70% of aspartame sales in the USA in early 2000s<br><br>*aspartame as main artificial sweetener in beverages in the 1980s and 1990s (before 1983: only saccharin, after 1983: mainly aspartame in soft drinks, 1998–2002: acesulfame-K, sucralose and neotame approved) | (Semi-) quantitative                                                     | 3 potentially aspartame-containing beverages: sugar-free or “diet” version of soda, fruit drinks, and iced tea<br><br>Tabletop aspartame-containing packets<br><br>No data on other potential sources: “diet” version of foods, such as yogurt, gelatin/pudding, ice cream and frozen desserts, and hot chocolate (50 mg or more aspartame per serving in the early 2000s) | Average daily consumption of aspartame in mg/day derived from consumption frequency, portion size and aspartame content<br><br>Values of aspartame content used (source: Nutrition Data System for Research) and literature search):<br><br>*per 100 g of beverage: 50 mg for diet soda, 14.95 mg for diet fruit drink, 25.55 mg for diet iced tea<br><br>*per tabletop packet: 35 mg<br><br>Categories of aspartame intake used in analyses: none, > 0 to < 100, ≥ 100 to < 200, ≥ 200 to < 400, ≥ 400 to < 600, ≥ 600 mg/day | Aspartame exposure assessed in 1995–1996 for the past 12 months, follow-up until 2000 | Potential co-exposure measured and considered in analyses: BMI, diabetes, alcohol, smoking, physical activity, caffeine                                                                                                                                                                                                                                                                                                                                                                                                                                | potential variations of the content of ASB in aspartame over time; only one dietary assessment at baseline: possible variations of ASB consumption over time; measurement errors<br><br>Differential unlikely: prospective cohort study; aspartame exposure assessed before cancer diagnosis<br><br>Non-differential likely: uncertainty regarding actual aspartame exposure (actual content of aspartame in the considered sources, aspartame content in other not considered sources); diet only assessed at baseline; measurement errors: assessment of the frequency of consumption of soft drinks and then of the diet version of these soft drinks |
| Liu et al. (2022)<br>Cancer mortality                   | Cohort (United Kingdom Biobank)                     | Validated web-based 24-hour dietary recall questionnaire (Oxford WebQ)<br><br>At least 1 questionnaire completed out of 5 maximum occasions over 1 yr (seasonal variations) between April 2009 and June 2012 (mean completed 24-hour dietary recalls (SD), n 2.2 (1.2))<br><br>Number of drinks of coffee in the previous 24hours, number of teaspoons of added sugar or artificial sweeteners (any brand)<br><br>Standard portion size (e.g. mug or cup) | What: artificially sweetened coffee<br><br>When: diet assessed between 2009 and 2012<br><br>Where: United Kingdom                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Semiquantitative                                                         | Artificial sweeteners added in coffee                                                                                                                                                                                                                                                                                                                                      | Classification as non-consumers, sole consumers (same kind of coffee over the dietary recalls: unsweetened, sugar-sweetened, artificially sweetened), overlapped consumers<br><br>Average number of drinks across multiple dietary recalls; one drink ≈ 250 mL; 5 groups: ≥ 0 to 1.5 drinks/d, ≥ 1.5 to 2.5 drinks/d, ≥ 2.5 to 3.5 drinks/d, ≥ 3.5 to 4.5 drinks/d, and ≥ 4.5 drinks/day (averages of 1, 2, 3, 4, and 5 or more drinks/d, respectively)                                                                        | Diet assessed in 2009–2012, follow-up until 2017–2018 (median of 7.0 yr)              | Potential co-exposure measured and considered in analyses: smoking, physical activity, BMI, waist circumference, hypertension, diabetes, long-standing illness, cholesterol-lowering drug, blood pressure drug, vitamin and mineral supplements, dietary intake of, total sugar, fresh fruit, vegetables, red meat, processed meat, alcohol, milk, tea, SSBs, ASBs, environmental factors (particulate matter, nitrogen dioxide, average 24-hour sound level of noise pollution, proximity to a major road, green space percentage, distance to coast) | Differential unlikely: cohort study; prospective assessment of exposure<br><br>Non-differential likely: no details on aspartame; only artificially sweetened coffee as potential sources of aspartame and no other sources; uncertainty whether the artificial sweeteners used contained aspartame; only one dietary assessment at baseline: possible variations of AS consumption over time; measurement errors                                                                                                                                                                                                                                         |
| Mahfouz et al. (2014)<br>Colorectal cancer              | Case–control                                        | FFQ Melbourne University? (8 items, 2 yr before cancer diagnosis)                                                                                                                                                                                                                                                                                                                                                                                         | What: soft drinks and artificial sweeteners<br><br>When: between 2010 and 2011<br><br>Where: Egypt                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Qualitative                                                              | Soft drinks, use of artificial sweeteners                                                                                                                                                                                                                                                                                                                                  | Consumption of soft drinks (yes/no)<br><br>Use of artificial sweeteners (yes/no)                                                                                                                                                                                                                                                                                                                                                                                                                                               | 2 yr before cancer diagnosis                                                          | Potential co-exposure measured and considered in analyses: red meat, preserved food, fast foods, smoking,                                                                                                                                                                                                                                                                                                                                                                                                                                              | Differential likely: retrospective assessment; case–control study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

**Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame**

| Reference and outcome                                  | What was the study design?          | What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)                                                                                                                                                                                                                                                                                                                                                          | What was the exposure context?<br>Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)<br>What was the agent under investigation?                                                       | Was estimate of exposure qualitative, semiquantitative, or quantitative? | Which exposure sources were assessed?                                                                                    | What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)?<br>(specify units)                                                                                                                                                                                                                                                                                                                                                        | What was the timing of exposure relative to the outcome?                                                                                                  | Which other potential carcinogens, confounders, or effect modifiers were assessed?                                                                                                                                                                                                                                                                                         | Was there potential for differential exposure misclassification?<br>Was there potential for non-differential exposure misclassification?<br>(Likely/unlikely)                                                                                                                                                                                                                                                                                                                               |
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|                                                        |                                     | Frequency of intake daily, weekly or monthly; number of servings                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                         |                                                                          |                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                           | spicy foods, processed meat, pickles, tea, obesity, alcohol                                                                                                                                                                                                                                                                                                                | Non-differential likely: no details on aspartame; qualitative assessment of soft drink consumption and use of artificial sweeteners; measurement errors                                                                                                                                                                                                                                                                                                                                     |
| Malik et al. (2019)<br>Cancer mortality                | Cohort (NHS and HPFS)               | Validated self-administered semiquantitative FFQ every 4 yr: since 1980 in the NHS and 1986 in the HPFS (61 items in 1980 to 131 and 166 items in subsequent questionnaire cycles)                                                                                                                                                                                                                                                                                                | What: artificially sweetened beverages<br>When: diet assessed from 1980–1986 to 2010, follow-up until 2014<br>Where: USA<br>Context: aspartame as primary artificial sweetener in ASBs                                                                  | Semiquantitative                                                         | Caffeinated, caffeine-free, and non-carbonated low-calorie or diet beverages                                             | Frequency of intake: < 1/mo, 1 to 4/mo, 2 to 6/wk, 1 to < 2/d, 2 to < 4/d, and ≥ 4/d<br><br>Update of dietary intakes at the beginning of each FFQ cycle (main analysis) and cumulative average (secondary analysis; mean intake from all FFQs up to the beginning of a follow-up interval); no update after report of diabetes, stroke, CHD, or cancer<br><br>Substitution of 1 serving/d of SSB with an equivalent amount of ASB                                                                      | Diet assessed every 4 yr from 1980 or 1986 until 2014<br><br>Secondary analyses with an 8-yr lag (exposures evaluated in relation to outcomes 8 yr later) | Potential co-exposure measured and considered in analyses: smoking, hormone use, alcohol, physical activity, multivitamins, aspirin, hypertension or hypercholesterolemia, intakes of whole grains, fruit, vegetables, and red and processed meat, diet quality (AHEI score), BMI, SSB, diabetes, CVD, cancer                                                              | Differential unlikely: cohort study; prospective assessment of exposure<br><br>Non-differential likely: no details on aspartame; only ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of ASB in aspartame over time; measurement errors                                                                                                                                                         |
| Mayne et al. (2006)<br>Oesophageal and gastric cancers | Population-based case-control study | Interviewer administered, in-person structured questionnaire (30% proxy interviews for cases, 3% for controls)                                                                                                                                                                                                                                                                                                                                                                    | What: diet soft drinks<br>Where: Connecticut (USA)<br>When: 1993–1995                                                                                                                                                                                   | Semiquantitative                                                         | Usual frequency of consumption of “diet soft drinks or soda” (per day, week, month, or year)                             | Diet soft drinks or soda, top 20% of consumers vs others                                                                                                                                                                                                                                                                                                                                                                                                                                                | 3–5 yr before diagnosis                                                                                                                                   | BMI, beer, wine, and liquor, meat; smoking                                                                                                                                                                                                                                                                                                                                 | Differential likely: case-control study; retrospective assessment<br><br>Non-differential likely: only ASB as a proxy measure                                                                                                                                                                                                                                                                                                                                                               |
| McCullough et al. (2014)<br>Lymphoid neoplasms         | Cohort (CPS-II Nutrition Cohort)    | Self-administered modified Willett FFQ (152 item) in 1999 and 2003<br><br>Artificially sweetened carbonated beverage consumption including subtypes (cola with caffeine, other carbonated beverages with or without caffeine): frequency categories ranging from “never” to “≥4 per day”, standard serving size (“1 glass, bottle, or can (355 mL)”)<br><br>Question regarding the use of aspartame packets (NutraSweet or Equal): frequency ranging from “never” to “≥6 per day” | What: aspartame<br>When: diet assessed in 1999 and 2003<br>Where: USA<br><br>Long-term soda consumption patterns examined from data collected in 1982 (CPS-II mortality cohort) but aspartame not calculated (not included in soft drinks at that time) | Quantitative                                                             | Artificially sweetened carbonated beverage and aspartame packets (main contributors)<br><br>Other sources not considered | Mean exposure over the past year (in mg/day) assessed in 1999 and 2003<br><br>Estimates from 1999 used to predict risk for 1999–2003, mean of 1999 and 2003 used to predict risk for 2003–2009<br><br>Continuous intake (per 50 mg/d), non-consumption and gender-specific quartiles<br><br>Values of aspartame assigned:<br><br>*180 mg/355 mL for low-calorie cola with caffeine, 90 mg/355 mL for other low-calorie soda with caffeine, and 70 mg/355 mL for other low-calorie soda without caffeine | Diet assessed in 1999, updated in 2003 and follow-up until 2009                                                                                           | Potential co-exposure measured and considered in analyses: smoking, BMI, diabetes, sugar-sweetened beverages, weight, waist circumference, physical activity, sitting time, hormone replacement therapy, NSAID, cholesterol-lowering medication, alcohol, intake of beef, processed meat, animal protein, total milk, saturated fat, fruits, vegetables, and tea or coffee | Differential unlikely: cohort study; aspartame exposure assessed before cancer diagnosis<br><br>Non-differential likely: uncertain sources of aspartame (values assigned to all beverages actually containing aspartame or not, aspartame being the most widely used sweetener in diet carbonated beverages in the USA); some sources of aspartame not considered (artificially sweetened non-carbonated beverages, yogurts, ice cream) but more minor compared to ASB and tabletop packets |



**Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame**

| Reference and outcome                                                                                                                 | What was the study design? | What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)                                                                                                                                                                                                                                                                                                                                                                                                                          | What was the exposure context?<br>Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)<br>What was the agent under investigation?                                                                                                                                                                                                                                                                                    | Was estimate of exposure qualitative, semiquantitative, or quantitative? | Which exposure sources were assessed?                                                                                                                                                                                                    | What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)?<br>(specify units)                                                                                                                | What was the timing of exposure relative to the outcome?                                                                                                           | Which other potential carcinogens, confounders, or effect modifiers were assessed?                                                                                                                                                                                                                                              | Was there potential for differential exposure misclassification?<br>Was there potential for non-differential exposure misclassification?<br>(Likely/unlikely)                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| McCullough et al. (2022)<br><br>Mortality from all cancers combined, obesity-related cancers combined, and 20 individual cancer types | Cohort (CPS-II)            | Question regarding the usual number of cups, glasses, or drinks per day, and duration for “diet soda or diet iced teas”<br><br>Previous intake inquired in case of a change in consumption during the past 10 yr<br><br>Exclusion of former drinkers (no current intake but non-zero amount for previous intake)                                                                                                                                                                                                                                  | What: artificially sweetened beverages<br><br>When: assessment at study baseline in 1982<br><br>Where: USA<br><br>Context: aspartame not included in ASB at the time of baseline questionnaire                                                                                                                                                                                                                                                                                       | Semiquantitative                                                         | Diet soda or diet iced teas                                                                                                                                                                                                              | *20 mg/packet of Nutrasweet or Equal<br><br>Usual daily consumption:<br><br>Categorical: never drinkers (no past or current consumption), < 1 drink/day, 1 drink/day, 2+ drinks/day<br><br>Continuous per 1 drink/day                                           | Questionnaire on ASB consumption in 1982, end of follow-up in 2016<br><br>Median follow-up of 27.7 yr<br><br>Follow-up censored at age 90 for men and 95 for women | Potential co-exposure measured and considered in analyses: smoking, red and processed meat, fruit and vegetable, alcohol consumption, SSB, for female cancers: estrogen, oral contraceptive<br><br>Other co-exposures considered but not included in analyses: aspirin, multivitamin, physical activity                         | Differential unlikely: cohort study; exposure assessed before cancer diagnosis<br><br>Non-differential likely: no details on aspartame, only ASB consumption as potential source of aspartame, ASB consumption assessed in 1982 at a time when ASB did not contain aspartame, no information on the stability of ASB consumption through the up to 34 yr of follow-up [some data in the CPS-II Nutrition cohort (McCullough et al., 2014) suggested a stable ranking of participants as regards ASB consumption between 1982 and 1999 for the subsample ( $n = 100\ 442$ ) providing data at both time points]. |
| Mullee et al. (2019)<br><br>Cancer mortality                                                                                          | Cohort (EPIC)              | Usual diet over the previous 12 months<br><br>Country-specific instruments developed and validated within the various source populations and including hundreds of country- and region-specific foods. These extensive self-administered quantitative dietary questionnaires collected usual portions and frequency of consumption of up to 260 food items food and drinks during different seasons of the year).<br><br>Soft drink consumption: number of glasses (typical glass sizes in each centre, $\approx 250$ mL) per month, week, or day | What: artificially sweetened soft drinks<br><br>When: diet assessed at inclusion between 1991 and 2000<br><br>Where: western European countries (Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom); data on artificially sweetened soft drinks not available in Spain, Italy (Florence, Turin, Ragusa, Varese) and Sweden (Umea)<br><br>Context: multiple European countries and associated context of consumption, no information on historical exposure | Semiquantitative                                                         | Carbonated/ soft/ isotonic drinks, and diluted syrups: “low-calorie or diet fizzy soft drinks”, “fizzy soft drinks, e.g. cola, lemonade”, and “fruit squash or cordial”<br><br>Total soft drinks: sugar-sweetened/artificially sweetened | Mean daily intakes over the past 12 months<br><br>Estimates per frequency of glasses consumed (< 1 glass per month, 1 to 4 glasses per month, > 1 to 6 glasses per week, 1 to < 2 glasses per day, or $\geq 2$ glasses per day), 1 glass = 250 mL               | Diet questionnaires covering the past year between 1991 and 2000<br><br>Mean (range) follow-up of 16.4 (11.1 to 19.2) years                                        | Potential co-exposure measured and considered in analyses: alcohol, smoking, BMI, physical activity, menopausal hormone therapy, dietary intakes of red and processed meats, coffee, fruit and vegetable juices, and fruits and vegetables, dietary fibre, sugar-sweetened soft drinks, cancer, heart disease, stroke, diabetes | Differential unlikely: cohort study; exposure assessed before cancer diagnosis<br><br>Non-differential likely: no details on aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline in a context of low consumption of ASB; potential variations of the content of ASB in aspartame; measurement errors                                                                                                                                                                                                                                                     |
| Navarrete-Muñoz et al. (2016)<br><br>Pancreatic cancer                                                                                | Cohort (EPIC)              | Usual diet over the previous 12 months<br><br>Country-specific instruments developed and validated within the various source populations and including hundreds of country- and region-specific foods. These extensive self-administered quantitative dietary questionnaires collected usual                                                                                                                                                                                                                                                      | What: artificially sweetened soft drinks<br><br>When: diet assessed at inclusion between 1991 and 2000<br><br>Where: western European countries (Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom); data on artificially sweetened soft drinks not available in Spain, Italy                                                                                                                                                                              | Quantitative                                                             | Carbonated/ soft/ isotonic drinks, and diluted syrups: “low-calorie or diet fizzy soft drinks”, “fizzy soft drinks, e.g. Cola, lemonade”, and “fruit squash or cordial”<br><br>Total soft drinks: sugar-sweetened/artificially sweetened | Mean daily intakes over the past 12 months<br><br>Estimates per 100 g/d and 12 oz (336 g/d) increments, for categorization into non-consumers and cohort-wide quintiles in consumers, and for alternative categorizations (i.e. 0.0, 0.1–124.9, 125.0–249.9, or | Diet questionnaires covering the past year between 1991 and 2000<br><br>Median follow-up of 11.6 y                                                                 | Potential co-exposure measured and considered in analyses: alcohol, physical activity, smoking, diabetes, BMI, intakes of red meat, fruit and vegetables, dietary sugar, coffee, folate, waist circumference, sugar-sweetened soft drinks, juice and nectar                                                                     | Differential unlikely: cohort study; exposure assessed before cancer diagnosis<br><br>Non-differential likely: no details on aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline in a context of low consumption of ASB;                                                                                                                                                                                                                                                                                                                                 |

**Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame**

| Reference and outcome                                                                                         | What was the study design?          | What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)                                                                                                                                         | What was the exposure context?<br>Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)<br>What was the agent under investigation?                         | Was estimate of exposure qualitative, semiquantitative, or quantitative? | Which exposure sources were assessed?                                                                                                                                                                                                                                | What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)?<br>(specify units)                                                                                                                                                                                                                                                                                                       | What was the timing of exposure relative to the outcome?                                                                                | Which other potential carcinogens, confounders, or effect modifiers were assessed?                                                                                                                        | Was there potential for differential exposure misclassification?<br>Was there potential for non-differential exposure misclassification?<br>(Likely/unlikely)                                                                                                      |
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|                                                                                                               |                                     | portions and frequency of consumption of up to 260 food items food and drinks during different seasons of the year).<br><br>Soft drink consumption: number of glasses (typical glass sizes in each centre, ≈ 250 mL) per month, week, or day                     | (Florence, Turin, Ragusa, Varese) and Sweden (Umea)<br><br>Context: multiple European countries and associated context of consumption, no information on historical exposure                                              |                                                                          |                                                                                                                                                                                                                                                                      | ≥ 250.0 g/d or < 1 glass/mo, 1–4 glasses/mo, > 1–6 glasses/wk, or ≥ 1 glass/d)                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                         |                                                                                                                                                                                                           | potential variations of the content of ASB in aspartame; measurement errors                                                                                                                                                                                        |
| Nomura et al. (1991)<br><br>Bladder                                                                           | Case–control study                  | Interviews, diet history of 29 food items consumed during a usual week (or usual month for less frequently consumed items), usual diet 1 yr before diagnosis                                                                                                     | What: artificially Sweetened beverages<br><br>Where: Hawaii<br><br>When: 1977 and 1986                                                                                                                                    | Qualitative                                                              | Artificially sweetened beverages, such as diet or low-calorie sodas<br><br>Use and frequency of saccharin, cyclamates and other artificial sweeteners (analysis for saccharin use only)                                                                              | Diet beverages: Non-user, User (1–2 can-years, 3+ can-years)                                                                                                                                                                                                                                                                                                                                                                                           | Usual diet 1 year before diagnosis                                                                                                      | Smoking                                                                                                                                                                                                   | Differential likely: case–control study; retrospective assessment, Interviewers not blinded to case–control status<br><br>Non-differential likely: only ASB as a proxy measure                                                                                     |
| Norell et al. (1986)<br><br>Pancreas                                                                          | Population-based case–control study | Self-administered questionnaire (and contact by telephone by a trained interviewer to clarify or complete items if necessary) including a binary question on use of artificial sweeteners                                                                        | What: artificial sweeteners<br><br>Where: Sweden<br><br>When: 1982–1984                                                                                                                                                   | Qualitative                                                              | Use artificial sweeteners                                                                                                                                                                                                                                            | Use artificial sweeteners (yes, no)                                                                                                                                                                                                                                                                                                                                                                                                                    | Subjects who had altered their dietary or other habits because of recent illness were asked to describe their habits before the illness | Not examined in multivariable models                                                                                                                                                                      | Differential likely: case–control study; retrospective assessment<br><br>Non-differential likely: only AS measured                                                                                                                                                 |
| Palomar-Cros et al. (2023)<br><br>Colorectal, breast, prostate, stomach cancer, chronic lymphocytic leukaemia | Case–control study                  | Self-administered, semiquantitative FFQ, 140 food items, assessing usual dietary intake during the previous year                                                                                                                                                 | What: Categorized intake of aspartame-containing products (low- or no-calorie soft drinks and tabletop sweeteners other than saccharin), and other AS (saccharin and Gaseosa).<br><br>Where: Spain<br><br>When: 2008–2013 | Semiquantitative                                                         | Consumption of AS was estimated from four questions in the FFQ:<br><br>(i) Low- or no-calorie soft drinks<br><br>(ii) Gaseosa (AS soft drink, contains saccharin and cyclamate)<br><br>(iii) Tabletop sweeteners (saccharin)<br><br>(iv) Tabletop sweetener (others) | Portions per day (derived from frequency data) of aspartame-containing vs other AS products.<br><br>Intake of each group of products were categorized for analysis as:<br><br>- Non-consumers<br>- Medium intake<br>- High intake<br><br>These categories were based on sex-specific quartiles among consumers in controls,<br><br>With 3rd and 4th quartiles used as medium and high intake and compared to non-consumers for both groups of products | Usual dietary intake during the previous year                                                                                           | Smoking, radiation exposure, total WCRF score (lifestyle), total energy intake, sugar intake<br><br>Models for intake of aspartame products were adjusted for consumption of products containing other AS | Differential likely: case–control study; retrospective assessment<br><br>Non-differential likely: two main sources considered, but rest of food supply not included (reported that other foods in Spain do contain AS e.g. Dairy products, during period studied). |
| Ringel et al. (2022)<br><br>Urinary tract cancers, bladder and kidney cancers                                 | Cohort (WHI-OS)                     | Question regarding the frequency of consumption of ASB during the past 3 months<br><br>Reference serving size (12 fl. oz can)<br><br>Nine frequency of servings: never or < 1/month, 1–3/month, 1/week, 2–4/week, 5–6/week, 1/day, 2–3/day, 4–5/day, and 6+/day. | What: artificially sweetened beverages<br><br>When: assessment 3 yr after study baseline in 1993–1998<br><br>Where: USA                                                                                                   | Semiquantitative                                                         | Diet drinks such as Diet Coke or diet fruit drinks                                                                                                                                                                                                                   | 3 categories: never or fewer than one serving per week (reference), one to six servings per week, and one or more servings per day (rare, frequent, and daily consumption)                                                                                                                                                                                                                                                                             | Questionnaire on ASB in 1996–2001, end of follow-up in 2020                                                                             | Potential co-exposure measured and considered in analyses: smoking, water consumption, BMI, history of hypertension, diet quality                                                                         | Differential unlikely: cohort study; exposure assessed before cancer diagnosis<br><br>Non-differential likely: no details on aspartame, only ASB consumption as potential source of aspartame, no information on the stability of ASB consumption over             |

**Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame**

| Reference and outcome                                | What was the study design? | What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)                                                                                                                                                                                                                                                                         | What was the exposure context?<br>Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)<br>What was the agent under investigation?                                                                        | Was estimate of exposure qualitative, semiquantitative, or quantitative? | Which exposure sources were assessed?                                                                                                                                                                                                                            | What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)?<br>(specify units)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | What was the timing of exposure relative to the outcome?                                                                                                                                                                    | Which other potential carcinogens, confounders, or effect modifiers were assessed?                                                                                                                                                             | Was there potential for differential exposure misclassification?<br>Was there potential for non-differential exposure misclassification?<br>(Likely/unlikely)                                                                                                                                                                            |
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| Romanos-Nanclares et al. (2021)<br>Breast cancer     | Cohort (NHS and NHS II)    | Validated semiquantitative FFQ (past year) administered every 4 yr since 1980 (NHS, 61 items in 1980, 116 items in 1984 and 1986, and $\geq 130$ items thereafter) or 1991 (NHSII, $\geq 130$ items)<br><br>Frequency of consumption for a standard 355 mL (12 oz) serving (1 glass/can/bottle) of each ASB: 9 possible responses ranging from “never/almost never” to “6 or more times per day” | What: ASB<br><br>When: diet assessed every 4 yr between 1980/1991 and 2016/2017<br><br>Where: USA                                                                                                                                                                        | Semiquantitative                                                         | Caffeinated, non-caffeinated, and non-carbonated low-calorie or diet beverages                                                                                                                                                                                   | Cumulative averages (mean intake from all FFQs up to the beginning of a 2-yr follow-up interval)<br><br>Estimates for categories of frequencies of intake: < 1/month, $\geq 1$ to $\leq 4$ /month, > 1 to < 7/week, and $\geq 1$ /day<br><br>Other models used: simple update (consumption reported on the most recent FFQ before each follow-up interval) and latency (consumptions reported at different latencies (i.e. 4–8, 8–12, 12–16, and 16–20 yr) before a cancer diagnosis)<br><br>Changes in consumption updated every 4 yr to estimate the risk in the subsequent 4-yr period: 5 categories (no change or relatively stable, increase or decrease from 1.0 serving/week to 0.50 serving/day, and increase or decrease by > 0.50 serving/day) | Diet assessed every 4 yr between 1980 and 2016 (NHS) or between 1991 and 2017 (NHSII)<br><br>Follow-up until 2006 for molecular subtypes<br><br>Cumulative average, simple update, latency or changes in consumption models | Potential co-exposure measured and considered in analyses: postmenopausal hormone, oral contraceptive, alcohol, physical activity, BMI at age 18, diet quality (AHEI score), SSB                                                               | Differential unlikely: cohort study; prospective assessment of exposure<br><br>Non-differential likely: no details on aspartame; only ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of ASB in aspartame over time; measurement errors      |
| Schernhammer et al. (2005)<br>Pancreatic cancer      | Cohort (NHS and HPFS)      | Validated self-administered semiquantitative FFQ every 4 yr: since 1980 in the NHS and 1986 in the HPFS<br><br>Diet soft drink consumption: 1 item (low-calorie carbonated drink) in 1980, 3 items (low-calorie cola, low-calorie caffeine-free cola, other low-calorie carbonated beverage) in 1984 and subsequent questionnaire cycles                                                         | What: artificially sweetened beverages<br><br>When: from 1980–1986 to 2000<br><br>Where: USA<br><br>Context: aspartame as primary artificial sweetener in ASBs                                                                                                           | Semiquantitative                                                         | Low-calorie carbonated drinks: low-calorie cola, low-calorie caffeine-free cola, other low-calorie carbonated beverage                                                                                                                                           | Cumulative average (average of all measures up to the start of each follow-up interval)<br><br>3 categories (less than once monthly, 1–12 times monthly, and > 3 times weekly)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Diet assessed every 4 yr since 1980/1986, follow-up until 2000                                                                                                                                                              | Potential co-exposure measured and considered in analyses: smoking, BMI, physical activity, diabetes, sugar-sweetened soft drinks, caffeine                                                                                                    | Differential unlikely: cohort study; prospective assessment of exposure<br><br>Non-differential likely: no details on aspartame; only some ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of ASB in aspartame over time; measurement errors |
| Schernhammer et al. (2012)<br>Lymphoma and leukaemia | Cohort (NHS and HPFS)      | Validated self-administered semiquantitative FFQ ( $\approx 130$ items)<br><br>Frequency of consumption (9 frequencies from never to $\geq 6$ times/d) with one serving size (355 mL) of 3 types of diet sodas: diet cola with caffeine, diet cola                                                                                                                                               | What: aspartame<br><br>Where: USA<br><br>When: diet sodas assessed every 4 yr since 1984 (NHS) and 1986 (both cohorts); tabletop sweeteners assessed every 4 yr since 1994<br><br>Context: aspartame approved in 1981, sole artificial sweetener in Diet Coke soda (most | Quantitative                                                             | Diet soda and aspartame packet (main contributors)<br><br>Other sources not considered: breakfast cereals collected by brand name but not considered in analysis (no breakfast cereals containing aspartame in the early years, only 4% at the end of follow-up) | Cumulative average (intakes updated after every FFQ with the mean of all reported intakes up to that time)<br><br>Assigned values of aspartame content:<br><br>*aspartame packet: 20 mg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Diet sodas: follow-up between 1984 (NHS), 1986 (HPFS) and 2006<br><br>Aspartame: follow-up between 1994 and 2006                                                                                                            | Potential co-exposure measured and considered in analyses: fruit and vegetable, multivitamins, alcohol, total sugar, saturated fat, animal protein, BMI, physical activity, smoking, hormone replacement therapy, diabetes, waist-to-hip ratio | Differential unlikely: cohort study; aspartame exposure assessed before cancer diagnosis<br><br>Non-differential likely: uncertainty regarding the content of the beverages in aspartame; other possible sources of aspartame not                                                                                                        |

**Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame**

| Reference and outcome                               | What was the study design?   | What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)                                                                                                                                                                                                                                                                                                                                                                                                                  | What was the exposure context?<br>Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)<br>What was the agent under investigation?                                                                                                                                                                                                                                                                                    | Was estimate of exposure qualitative, semiquantitative, or quantitative? | Which exposure sources were assessed?                                                                                                                                                                                                                                                                                                                                                       | What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)?<br>(specify units)                                                                                                                                                                                                                | What was the timing of exposure relative to the outcome?                                                               | Which other potential carcinogens, confounders, or effect modifiers were assessed?                                                                                                                                                                                                                                        | Was there potential for differential exposure misclassification?<br>Was there potential for non-differential exposure misclassification?<br>(Likely/unlikely)                                                                                                                                                                                                                     |
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|                                                     |                              | without caffeine, and other diet soda<br><br>Dietary collected every 4 yr since 1984 (NHS) and 1986 (both cohorts)<br><br>Use of aspartame sweeteners added at the table (Nutrasweet and Equal) assessed every 4 yr since 1994                                                                                                                                                                                                                                                                                                            | commonly used diet soda) from 1983, most other diet sodas in the 1980s used both aspartame and saccharin; aspartame most broadly used in sodas from 1992<br><br>Lifetime exposure to aspartame from diet sodas captured                                                                                                                                                                                                                                                              |                                                                          |                                                                                                                                                                                                                                                                                                                                                                                             | *diet soda: weighted average of the representative sodas in that category (70–180 mg/serving)<br><br>Zero intakes as the lowest category and cohort specific exact quartiles                                                                                                                                                                                    |                                                                                                                        |                                                                                                                                                                                                                                                                                                                           | considered (although more minor)                                                                                                                                                                                                                                                                                                                                                  |
| Singh et al. (2020)<br><br>Thyroid cancer           | Case–control study           | Telephone based, self-report questionnaire on use of artificial sweeteners                                                                                                                                                                                                                                                                                                                                                                                                                                                                | What: Aspartame consumption amount<br><br>Where: USA<br><br>When: Cases from between 2004–2014, with duration of exposure reported by subject, average reported duration of exposure = 5 yr.<br><br>Context: Retrospective assessment of dose based on current food composition data                                                                                                                                                                                                 | Quantitative                                                             | Artificial sweetener consumption as tabletop sweetener and beverages (beverages included in assessment were as carbonated beverages, multiple colas, Sprite, Mountain Dew, Fresca)<br><br>Consumption of artificial sweetener in the form of snacks/ice creams was not considered.<br><br>Intake of the mixture of artificial sweeteners in products was assessed and used in the analysis. | Total amount and duration of artificial sweetener consumed                                                                                                                                                                                                                                                                                                      | Average duration of 5 yr before diagnosis                                                                              | Other co-exposures: BMI; alcohol; irradiation in childhood                                                                                                                                                                                                                                                                | Differential likely: case–control study; retrospective assessment<br><br>Non-differential likely: no specific assessment of aspartame alone, only total artificial sweeteners and only in beverages                                                                                                                                                                               |
| Stepien et al. (2016)<br><br>Hepatocellular cancers | Cohort (EPIC)                | Usual diet over the previous 12 months<br><br>Country-specific instruments developed and validated within the various source populations and including hundreds of country- and region-specific foods. These extensive self-administered quantitative dietary questionnaires collected usual portions and frequency of consumption of up to 260 food items food and drinks during different seasons of the year).<br><br>Soft drink consumption: number of glasses (typical glass sizes in each centre, ≈ 250 mL) per month, week, or day | What: artificially sweetened soft drinks<br><br>When: diet assessed at inclusion between 1991 and 2000<br><br>Where: western European countries (Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom); data on artificially sweetened soft drinks not available in Spain, Italy (Florence, Turin, Ragusa, Varese) and Sweden (Umea)<br><br>Context: multiple European countries and associated context of consumption, no information on historical exposure | Quantitative                                                             | Carbonated/ soft/ isotonic drinks, and diluted syrups: “low-calorie or diet fizzy soft drinks”, “fizzy soft drinks, e.g. Cola, lemonade”, and “fruit squash or cordial”<br><br>Total soft drinks: sugar-sweetened/artificially sweetened                                                                                                                                                    | Mean daily intakes over the past 12 months<br><br>Estimates per serving (330 g, equivalent to a soft drink can size in Europe: 330 mL)                                                                                                                                                                                                                          | Diet questionnaires covering the past year between 1991 and 2000<br><br>11.4 yr of follow-up                           | Potential co-exposure measured and considered in analyses: smoking, alcohol (at recruitment and lifetime pattern), BMI, physical activity, diabetes, liver function, waist-to-hip ratio, intakes of sugar, meats, fish, fruit and vegetables, other non-alcoholic beverages intake (i.e. Coffee and tea), gallstones, SSB | Differential unlikely: cohort study; exposure assessed before cancer diagnosis<br><br>Non-differential likely: no details on aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline in a context of low consumption of AS soft drinks; potential variations of the content of AS soft drinks in aspartame; measurement errors |
| Wang et al. (2021)<br><br>Colorectal cancer         | Cohort (NHS, NHSII and HPFS) | Validated self-administered semiquantitative FFQ every 4 yr: since 1984 (NHS), 1986 (HPFS) and 1991 (NHSII)                                                                                                                                                                                                                                                                                                                                                                                                                               | What: sulfur microbial diet score<br><br>When: diet assessed every 4 yr since 1984 (NHS), 1986 (HPFS) and 1991 (NHSII) until 2014 (HPFS), 2016 (NHS) and 2017 (NHSII)<br><br>Where: USA                                                                                                                                                                                                                                                                                              | Quantitative                                                             | Low-calorie beverages                                                                                                                                                                                                                                                                                                                                                                       | Sulfur microbial diet score: weighted sum of standardized consumption of food groups with positive weights for low-calorie beverages, French fries, red meats, and processed meats, and negative weights for fruits, yellow vegetables, whole grains, legumes, leafy vegetables, and cruciferous vegetables (positive and negative correlation with most of the | Diet assessed every 4 yr since 1984 (NHS), 1986 (HPFS) and 1991 (NHSII) until 2014 (NHS), 2016 (HPFS) and 2017 (NHSII) | Potential co-exposure measured and considered in analyses: BMI, smoking, physical activity, aspirin, NSAID, menopausal hormone therapy, western dietary pattern                                                                                                                                                           | Differential unlikely: cohort study; prospective assessment of exposure<br><br>Non-differential likely: no details on aspartame; ASB (potential source of aspartame) as a component of the sulfur microbial diet score; uncertainty regarding the content of ASB in aspartame; potential variations of the content of ASB in aspartame over time; measurement errors              |

**Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame**

| Reference and outcome                                           | What was the study design?             | What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)                                                                                                                                                                                                                                                                                                                                      | What was the exposure context?<br>Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)<br>What was the agent under investigation?                                                                                                                                                                                                                                                                                                                                                                          | Was estimate of exposure qualitative, semiquantitative, or quantitative? | Which exposure sources were assessed?                                                                                                                                                                                                    | What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)?<br>(specify units)                                                                                                                                                                           | What was the timing of exposure relative to the outcome?                                                                                          | Which other potential carcinogens, confounders, or effect modifiers were assessed?                                                                                                                                                                                              | Was there potential for differential exposure misclassification?<br>Was there potential for non-differential exposure misclassification?<br>(Likely/unlikely)                                                                                                                                                                                                                     |
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|                                                                 |                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                          |                                                                                                                                                                                                                                          | sulfur-metabolizing bacteria respectively)<br><br>Cumulative average of the sulfur microbial diet score (updated at each questionnaire cycle), categorization into quintiles                                                                                                                                               |                                                                                                                                                   |                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                   |
| You et al. (2022)<br>Lung cancer<br>All cancer                  | Prospective cohort study (PLCO cohort) | Diet history questionnaire: Food frequency questionnaire with 156 items                                                                                                                                                                                                                                                                                                                                                                                       | What: Diet soft drinks<br><br>Where: 10 study centres in the USA<br><br>When: Baseline data collected 1993–2001; follow-up until 2009; median follow-up time 11.3yrs                                                                                                                                                                                                                                                                                                                                                                                                       | Qualitative                                                              | Daily gram of consumption of regular and diet/sugar-free soft drinks using frequency and serve size                                                                                                                                      | Consumption of soft Drink was categorized as:<br><br>1. “None”: No regular drinks or diet/sugar-free soft drinks;<br><br>2. “Regular only”: Only regular soft drinks;<br><br>3. “Diet only”: only diet/sugar-free soft drinks;<br><br>4. “Both”: Both regular and diet/sugar-free soft drinks.                             | Baseline dietary data collected referring to the previous 12 months.<br><br>Patients with any cancer before baseline excluded from this analysis. | Included in multivariable models: (BMI) types at baseline, smoking status, physical activity status, daily energy consumption, red meat, fruits, vegetables and coffee, alcohol consumption, estrogen use (females only)                                                        | Differential unlikely: cohort study with assessment before diagnosis<br><br>Non-differential likely: only ASB as a proxy measure                                                                                                                                                                                                                                                  |
| Yuan et al. (2022)<br>Colorectal cancer incidence and mortality | Cohort (NHS and HPFS)                  | Validated self-administered semiquantitative FFQ (past year) every 4 yr: since 1980 (NHS) and 1986 (HPFS)<br><br>Frequency of consumption of 61 items (1980) up to 131–169 items in 1984<br><br>9 possible responses ranging from “never or less than once per month” to “6 or more times per day”                                                                                                                                                            | What: ASB<br><br>When: diet assessed every 4 yr since 1980 (NHS) or 1986 (HPFS) until 2014<br><br>Where: USA                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Quantitative                                                             | Caffeinated, caffeine-free, and non-carbonated low-calorie or diet beverages                                                                                                                                                             | Substitution of 1 serving of SSBs per day with an equivalent amount of ASBs; no estimates for ASB as such<br><br>Cumulative average intake (average of all available FFQs from baseline until the current survey cycle)<br>Average intake during the most recent 10 y (recent period) and from > 10 y ago (distant period) | Diet assessed every 4 yr since 1980 (NHS) or 1986 (HPFS) until 2014<br><br>Secondary analyses with recent and distant periods                     | Potential co-exposure measured and considered in analyses: BMI, physical activity, smoking, alcohol, aspirin, diabetes, menopausal hormone therapy, intakes of dietary fibre, total calcium, total folate, red meat, and processed meat, diet quality (AHEI-2010), fruit intake | Differential unlikely: cohort study; prospective assessment of exposure<br><br>Non-differential likely: no details on aspartame; only ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of ASB in aspartame over time; measurement errors                                               |
| Zamora-Ros et al. (2022)<br>Thyroid cancer                      | Cohort (EPIC)                          | Usual diet over the previous 12 months<br><br>Country-specific instruments developed and validated within the various source populations and including hundreds of foods. These extensive self-administered quantitative dietary questionnaires collected usual portions and frequency of consumption of up to 260 food items food and drinks during different seasons of the year).<br><br>Soft drink consumption: number of glasses (typical glass sizes in | What: artificially sweetened soft drinks<br><br>When: diet assessed at inclusion between 1991 and 2000<br><br>Where: western European countries (Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom); data on artificially sweetened soft drinks not available in Spain, Italy (Florence, Turin, Ragusa, Varese) and Sweden (Umea)<br><br>Context: multiple European countries and associated context of consumption, no information on historical exposure; consumption of ASB relatively low in the 90s (baseline): < 25% of total soft drinks) | Quantitative                                                             | Carbonated/ soft/ isotonic drinks, and diluted syrups: “low-calorie or diet fizzy soft drinks”, “fizzy soft drinks, e.g. Cola, lemonade”, and “fruit squash or cordial”<br><br>Total soft drinks: sugar-sweetened/artificially sweetened | Mean daily intakes over the past 12 months<br><br>Estimates per 100 mL/d and for non-consumers/tertiles of consumers                                                                                                                                                                                                       | Diet questionnaires covering the past year between 1991 and 2000<br><br>Mean follow-up of 14 yr                                                   | Potential co-exposure measured and considered in analyses: BMI, smoking, physical activity, oral contraceptive, infertility problems, alcohol                                                                                                                                   | Differential unlikely: cohort study; exposure assessed before cancer diagnosis<br><br>Non-differential likely: no details on aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline in a context of low consumption of AS soft drinks; potential variations of the content of AS soft drinks in aspartame; measurement errors |

**Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame**

| Reference and outcome                   | What was the study design? | What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)                                                                                                                                                                                      | What was the exposure context?<br>Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)<br>What was the agent under investigation?    | Was estimate of exposure qualitative, semiquantitative, or quantitative? | Which exposure sources were assessed?                           | What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)?<br>(specify units)                                                                                                                                      | What was the timing of exposure relative to the outcome?                     | Which other potential carcinogens, confounders, or effect modifiers were assessed?                                                                                                                                                                                                                         | Was there potential for differential exposure misclassification?<br>Was there potential for non-differential exposure misclassification?<br>(Likely/unlikely)                                                                                                                                                                    |
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| Zhang et al. (2021)<br>Cancer mortality | Cohort (NHANES)            | each centre, ≈ 250 mL) per month, week, or day<br>24-hour dietary recalls: before 2003, only one 24-hour dietary recall administered in-person, since 2003, two 24-hour dietary recalls (1 in-person and 1 by telephone after 3–10 days)<br>Trained investigators<br>Main Food List with over 2600 food items | What: artificially sweetened beverages<br>When: inclusion between 1999 and 2014, follow-up until 2015<br>Where: USA<br>Context: ASB consumptions increased from 1999 to 2006 but declined afterwards | Semiquantitative                                                         | Sugar-free soft drinks and carbonated water (no sugar, only AS) | Mean intake from up to two 24-hour dietary recalls<br>Standard 12-oz serving defined<br>Estimates per 12-oz serving/d and for categories: none, > 0 to < 1 serving/d, 1 to < 2 servings/d, and ≥ 2 servings/d<br>Substitution of one serving/d of SSB with equivalent amounts of ASBs | Diet estimated once between 1999 and 2014, follow-up (registries) until 2015 | Potential co-exposure measured and considered in analyses: alcohol, smoking, physical activity, BMI, high-cholesterol, hypertension, diabetes, CVD, cancer, diet quality (HEI-2015), intakes of major food groups (i.e. Vegetable, fruit, whole grain, red meat, and processed meat), macronutrients, SSBs | Differential unlikely: cohort study; prospective assessment of exposure<br>Non-differential likely: no details on aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline through 1 or max. 2 24-hour recalls; potential variations of the content of ASB; measurement errors |

acesulfame-K, acesulfame potassium; AS, artificial sweetener; ASB, artificially sweetened beverage; BMI, body mass index; CPS, Cancer Prevention Study; CVD, cardiovascular disease; d, day(s); EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HPFS, Health Professionals Follow-up Study; IBD, inflammatory bowel disease; NHANES, National Health and Nutrition Examination Survey; NIH-AARP, National Institutes of Health-American Association of Retired Persons Diet and Health Study; NHS, Nurses' Health Study; NNS, non-nutritive sweetener; NR, not reported; PLCO, Prostate Lung, Colorectal and Ovarian cancer screening trial; SD, standard deviation; SSB, sugar-sweetened beverage; US, United States; UTD, urinary tract disease; vs, versus; wk, week(s); yr, year(s).

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