The Center for Science in the Public Interest (CSPI) thanks the Carcinogen Identification Committee (CIC) and the Office of Environmental Health Hazard Assessment (OEHHA) for the opportunity to submit comments on the Prioritization of Aspartame for Future CIC Review.

CSPI is a non-profit consumer education and advocacy organization that since 1971 has been working to improve the public’s health through better nutrition and food safety policies. CSPI’s work is supported primarily by its 600,000 subscribers to its Nutrition Action Healthletter, the nation's largest-circulation health newsletter. CSPI is an independent organization that does not accept any government or corporate funding.

CSPI has a long-standing commitment to addressing American’s overconsumption of sugar and its impact on obesity, diabetes, heart disease, tooth decay, and other health problems. CSPI also regularly evaluates and rates the safety of additives, rating most additives as safe, but campaigning for federal bans on others. We welcome safe artificial sweeteners that would help consumers lose weight. However, we advise consumers to avoid aspartame because of the compelling evidence that it causes cancer.

CSPI strongly urges the CIC and OEHHA to make aspartame a high priority for future CIC review. That would be consistent with the decision of the International Agency for Research on Cancer, which recently designated aspartame a high priority for review. We also urge the CIC to not defer to the flawed review by the European Food Safety Authority. Finally, we provide additional references that we urge the CIC to consider in its future review of aspartame.

Widespread, High Exposure to Aspartame
Aspartame is one of the most widely consumed artificial sweeteners in the United States and the world. The primary source of exposure to aspartame in the United States is diet soft drinks, including Coke Zero, Diet Coke, Pepsi Zero Sugar, Diet Pepsi (Classic Sweetener Blend), Diet Mtn Dew, Red Bull Sugar Free, Sam’s Choice Diet Cola, and others. The OEHHA summary on aspartame states that typical consumption is 2-3 mg/kg/day, but can be much higher. Indeed, that amount would be reached by a 60 kg person drinking one 12-
ounce can of diet soda per day, but aspartame consumption was reported to be as high as 3,400 mg per day in the NIH-AARP Diet and Health Study (about 19 cans of soda). In addition to diet soda, aspartame is commonly consumed in tabletop sweeteners used in coffee or tea, desserts (e.g., Jell-O sugar-free gelatins and instant puddings, Popsicle sugar-free ice pops), candy and gum (e.g., Breath Savers Sugar-Free Peppermint Mints, Stride Spearmint Sugar-Free Gum), and other foods, as well as vitamins, toothpaste, and pharmaceuticals.

Positive Findings of Carcinogenicity in Three Independent Animal Studies and a Human Cohort Study
Three independent rodent bioassays, in two species, both sexes, found aspartame to cause cancer at multiple sites. These studies were published in peer-reviewed journals, two published by the U.S. government. They used more animals, followed over their lifetimes, with two including in utero exposure, and thus were considerably more sensitive than previous animal studies conducted by industry.

Among the cancers induced in Sprague Dawley rats by aspartame are transitional-cell carcinomas of the renal pelvis/ureter, which are extremely rare and so the finding is highly significant. In the first independent bioassay of aspartame in rats, those tumors were found in 21/1500 aspartame treated animals, versus none in controls. Those tumors were found in only 2/2,669 control Sprague-Dawley rats in 17 studies and 1/1,060 control Fischer 344 rats in 10 studies. These carcinomas in female rats exposed to aspartame showed a positive trend (p<0.05), and there was a significant increase (p<0.05) in high-dose females. Furthermore, statistically significant increases of dysplastic lesions plus carcinomas of renal pelvis/ureter were seen in the four top doses, with a positive trend in females (p<0.01).

Lymphoma and leukemia were the most commonly observed cancers in the two independent rat studies. The finding in a recent prospective cohort study of a slight but significant increased risk in incidence of similar (lymphohematopoietic) tumor types as seen in those two animal studies lends a modicum of additional support to the conclusion that aspartame is likely carcinogenic in humans.

That prospective cohort study also contains a clue as to a possible mechanism of action for aspartame. The authors hypothesized that the sex differences they observed in lymphohematopoietic cancers (the increased risk in men for non-Hodgkin’s lymphoma and multiple myeloma in men, not observed in women) might have been due to the recognized higher enzymatic activity of alcohol dehydrogenase type I (ADH1) in men, which possibly induced higher conversion rates from methanol to formaldehyde. Several researchers have noted that aspartame metabolizes to formaldehyde. Formaldehyde has been classified as a human carcinogen, and, like aspartame, causes lymphohematopoietic and other cancers in animals. (The evidence that formaldehyde causes those cancers in humans came long after the studies in animals). Studies performed by the RI laboratory as
well as other laboratories corroborate that other chemicals that metabolize to formaldehyde, namely MTBE and methanol, cause cancer. Furthermore, since concurrent alcohol (ethanol) consumption inhibits methanol metabolism, the authors stratified the results in men by alcohol intake. They assumed that men with lower regular alcohol consumption would have higher formaldehyde conversion rates if they consumed large amounts of diet soda, and consequently, higher cancer risk. In fact, this was the case. Risks of non-Hodgkin’s lymphoma, multiple myeloma, and leukemia were higher in men with a lower alcohol intake. Similarly, Soffritti notes that the differing results between male and female rats exposed to aspartame (more lymphohematopoietic cancers observed in females vs. males) may be due to the higher activity of ADH1 in female rats than in male rats.

**Studies Finding No Evidence of Carcinogenicity of Aspartame Do Not Provide Convincing Evidence of Non-Carcinogenicity and Do Not Outweigh Positive Findings**

The five industry-sponsored negative chronic-carcinogenicity rodent studies reporting no evidence of carcinogenicity had lower power and sensitivity than the independent studies reporting positive evidence of carcinogenicity. The industry studies used 36-40 animals/sex/dose and thus fell short of the recommended 50 animals/sex/dose and were of shorter duration. Most of these old studies were only recently made publicly available (via the EFSA website) and a recent analysis noted other important limitations (e.g., statistically significant decreases in feed consumption, body weight, and survival may have limited full expression of carcinogenic effects).

The first (2006) independent bioassay used 100-150 animals/sex/group, for a total of 1,800 animals (compared to the total of 280-440 animals/study in the industry studies). The second used 70 animals/sex/treatment group, and the third used 62-122/sex/group. The negative findings from a series of three transgenic mouse assays are not compelling. NTP transgenic studies are no longer used for cancer evaluation screening, because they are not considered reliable. According to NTP, “there is uncertainty whether the study possessed sufficient sensitivity to detect a carcinogenic effect.”

Two epidemiology studies found negative results, but those studies have important limitations. In particular, a large epidemiology study by Lim et al. had serious weaknesses. For example, aspartame was not approved until the subjects were in their late 30s to 50s or older, and there were poor data on consumption levels. Few of these older adults drank large amounts of diet soda. Studies in which subjects consumed aspartame beginning early in life and lasting throughout their lifetimes, and using large numbers of high-exposure subjects, are much more likely to detect carcinogenic potential than studies without these characteristics. It is unlikely that the Lim study could have detected any carcinogenic potential of aspartame.

A second study, by McCullough, et al., is not quite as large as the positive study by Schwernhammer et al., which may explain why it failed to detect a dose-response trend in
lymphoid neoplasms. It is difficult to design epidemiological studies to detect the carcinogenic potential of additives, which are used in relatively small amounts, because dosages are ill-defined, risks are low, and there are many, confounding variables. That is why animal studies are traditionally relied on to detect the potential of chemicals to cause cancer in humans.

There Are No Valid Reasons to Dismiss Results of the Three Recent Independent Animal Studies on Aspartame

The three independent rodent bioassays finding that aspartame caused cancer were conducted by the Ramazzini Institute (RI). There is compelling evidence that

1. The RI produces reliable results largely consistent with those of NTP and other laboratories.\(^1\)
2. The protocols used by the RI provide advantages for identification of chemical-related neoplasia not obtained from other bioassays.\(^2\)
3. The lymphomas/leukemias (L/L) observed in RI rat studies of aspartame are not induced by infection, as previously hypothesized.\(^3\)
4. Generally speaking, L/L in aging rats are challenging to measure via light microscopy, and there have been differences in opinions on the magnitude of the cancer response for lymphomas/leukemias in the few RI studies where these cancers have been detected in rats.\(^4\) These differences in opinion create uncertainties for quantitative risk assessment, but do not create uncertainty in identifying carcinogenic hazards. Currently, a collaborative effort between NTP and the RI is underway to better characterize L/L in RI rats.\(^5\)
5. An NIEHS Pathology Working Group (PWG) that focused specifically on the first RI study of aspartame stated “diagnoses of lymphatic and histocytic neoplasms in the cases reviewed were generally confirmed.”\(^6\)
6. Aspartame caused cancers other than L/L in 3 RI animal bioassays, including rare kidney tumors that are highly significant.\(^7\)
7. Since aspartame causes cancer in animals, it should be presumed to cause cancer in humans.\(^8\) The most powerful epidemiological study on the carcinogenicity of aspartame, though such studies have obvious limitations, supports the animal findings.

EFSA Evaluation is Not the Final Word

A recent re-evaluation by the European Food Safety Authority (EFSA) was seriously flawed. It glossed over key findings from the independent animal studies, overlooked weaknesses of negative studies, and ignored information and analysis by U.S. government scientists relevant to interpreting RI data, and other relevant studies, including most of those listed in the next section.\(^9\) The EFSA re-evaluation was sharply criticized for bias and conflicts of interest\(^10\) and for cutting and pasting sections of an industry review into an earlier version of the report.\(^11\)
Relevant References Not Listed in OEHHA Preliminary Summary on Aspartame That Should Be Considered

In the course of CSPI’s investigation into aspartame, we endeavored to review all relevant published articles and reports relating to the methodology and the interpretation of findings from the Ramazzini Institute (RI). We urge that the following sources not included in the OEHHA Preliminary Summary of Aspartame be considered by OEHHA and the CIC:


The Pathology QA Review and PWG Coordinator’s Report for RI studies add important detail to the Summary Report listed. Together these comprise the most comprehensive review of RI laboratory practices and pathology evaluations available. The 2011 PWG declared the RI to be “a well-organized, clean facility”, where staff “apply meticulous detail to the necropsy and to the recording, collecting, and archiving of materials and tissues.” The Pathology QA Reviews and PWG Coordinator’s Reports documented that all slides required were present, histologic quality of the sections were considered “very good” by the QA pathologist, “with no deficiencies that interfered with the examination or the interpretation of histopathologic changes that were present,” and “neither the occasional cases with tissue autolysis nor the use of alcohol fixation presented diagnostic difficulties.”


This PWG focused specifically on the first RI rat study of aspartame and found that “diagnoses of lymphatic and histocytic neoplasms in the cases reviewed were generally confirmed.”

This article and responses to letters to the editor provide compelling evidence to reject the hypothesis that infection in RI rats, not aspartame, caused lymphomas/leukemias in the first RI study (2006), as some reviewers have alleged.


Compares results of numerous RI chronic bioassays with those conducted by the U.S. National Toxicology Program, finding remarkably consistent results. Notes that these two programs are the largest, longest-existing, and most well-established bioassay programs in the world.


Notes that the protocols used by the RI provide advantages for identification of chemical-related neoplasia not obtained from other bioassays. Concludes that RI bioassay results for cancer endpoints other than respiratory tract lymphoma/leukemia, and inner ear and cranium neoplasms, are generally consistent with those of NTP and other laboratories. Provides several plausible explanations why the PWG panel reported fewer lymphomas than RI pathologists or the QA pathologist, including that the PWG panel did not also review potentially corroborating diagnoses in other tissues. This paper concluded that since a diagnosis of increased lymphomas/leukemias occurred in a minority of RI studies (about 5 percent), and since there is consistency of diagnoses between RI and non-RI studies (e.g., for chemicals metabolized to formaldehyde), this suggests that associations between chemical exposures and lymphomas/leukemias have not been regularly misidentified in RI studies.

Thank you for considering these comments.
ENDNOTES

7 Schernhammer 2012
   (b) Soffritti 2006 (endnote 4a)
   (c) Schernhammer 2012 (endnote 6)
9 US Food and Drug Administration, 2006. Toxicological Principles for the Safety Assessment of Food Ingredients: Redbook 2000. IV.C.6 Carcinogenicity Studies with Rodents states, “It is recommended that carcinogenicity studies begin with at least 50 animals per sex per group.”
   (b) Gift 2013 (endnote 8)
12 (a) Gift 2013 (endnote 8)
   (b) Gift 2013 (endnote 8)
14 (a) Gift 2013 (endnote 8)

15 Soffriti M et al, 2014. (endnote 10)
17 Soffriti 2006, Soffriti 2007, Soffriti 2010 (endnote 4); Soffriti 2014 (endnote 10).
19 Comments submitted by Center for Science in the Public Interest, Kathleen Burns PhD, Director, Sciencecorps, James Huff PhD, Guest Researcher, National Institute of Environmental Health Sciences (for affiliation purposes only), Ronald Melnick PhD, Ron Melnick Consulting LLC on Draft scientific opinion on the re-evaluation of aspartame as a food additive, EFSA Panel on Food Additives and Nutrient Sources added to Food Consultation.  Available at http://www.cspinet.org/new/pdf/aspartame-efsa-final-comments-21913.pdf
20 Millstone, E. EFSA on Aspartame January 2013: A lost, but not the last, opportunity.  Submitted 2/22/13 to Ms. Claudia Heppner, Head of EFSA “Food Ingredients and Packaging” Unit and Mr. George Kass, Senior Scientific Officer, EFSA “Food Ingredients and Packaging” Unit.  At http://sro.sussex.ac.uk/43821/1/EM_Letter_to_EFSA_on_Aspartame_22Feb2013.pdf.  The panel’s composition changed slightly (two additional members were added) by the time the final report was published.  Accessed October 24, 2016.