

Prioritizing Aspartame

CARCINOGEN IDENTIFICATION COMMITTEE
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Center for Science in the Public Interest

- ✓ Independent science-based advocacy organization working to improve public health
 - ✓ Ca. 600,000 subscribers; No ads in our Nutrition Action Healthletter
 - ✓ No industry or government funding
- ✓ CSPI has long been active in efforts to reduce sugar consumption. We welcome safe low/no calorie sweeteners.
- ✓ We are not “anti-additive.” We rate most additives as safe. See <http://www.cspinet.org/reports/chemcuisine.htm>



CSPI's Bottom Line: Make Aspartame a **High Priority** for Future CIC Review

- ✓ Consistent with IARC's recent decision to designate aspartame a **high priority** for review
- ✓ One of Most Widely Consumed Artificial Sweeteners
- ✓ Positive Findings in **3** Animal Studies (Two Species, Both Sexes, **Multiple Sites**); Supportive Human Evidence
- ✓ Negative Studies Do Not Provide Convincing Evidence of Non-Carcinogenicity, Don't Outweigh Positive Findings
- ✓ Do Not Rely on Flawed EFSA Review

High Exposure: much higher than OEHHA's 2-3 mg/kg/day [**140-210 mg per day**])

From the



“What are some facts about aspartame?”

- ✓ In the NIH-AARP Diet and Health Study, aspartame consumption ranged from 0 to **3400 mg per day** (about 19 cans of soda at the high end; however, the upper limit is not absolute because investigators asked multiple-choice questions on frequency and the highest option was "6-plus times a day"). There are **180 mg of aspartame in a 12 ounce can of diet soda.**”

Positive in **Three** Animal Studies by an Independent Lab

- ✓ Published in peer-reviewed journals
- ✓ Two published in U.S. government-sponsored journal
- ✓ Far superior to old industry studies
 - ✓ Much larger
 - ✓ Followed over their lifetimes
 - ✓ Two included *in utero* exposure

Is the Ramazzini Institute (RI) a Credible, Professional Organization? **YES**

Rumors abound, but what is the evidence?

The 2011 Summary Report of the NTP-EPA-Sponsored Review + the individual Pathology Working Group reports for RI studies = the most comprehensive review of RI laboratory practices and pathology evaluations available

- ✓ All slides required were present
- ✓ The SOPs, GLP documents, and necropsy records were **within GLP expectations.**"
- ✓ "Histologic quality of the sections **"very good"**

Is the Ramazzini Institute a Credible, Professional Organization? **YES**

- ✓ "The two largest, longest-existing, and most well-established bioassay programs in the world are the Ramazzini Foundation and the National Toxicology Program"
- ✓ a comparative review found **remarkably consistent results** (e.g., benzene, methylene chloride, TCE)

Huff, Ann NY Acad Sci 2002 Dec; 982:208-30

Are Ramazzini Institute Cancer Bioassays Well-Designed? **YES**

“ Although the protocols characteristic of RI studies can cause interpretive challenges, aspects of the RI design, including **gestational exposure, lifespan observation, and larger numbers of animals and dose groups**, may impart advantages that provide chemical risk assessors with **valuable insights for the identification [of] chemical-related neoplasia not obtained from other bioassays.**”

Gift et al. *Environ Health Perspect* 2013; 121:1253-1263.

Are Ramazzini Institute Tumor Diagnoses Reliable? **YES**

- ✓ A 2004 NIEHS PWG Report of the first RI study **on aspartame** states “The diagnoses of lymphatic and histocytic neoplasms in the cases reviewed were **generally confirmed.**”
- ✓ In the 2011 NTP/EPA Review of RI studies (not aspartame), QA pathologists of the PWG and the PWG itself agreed with diagnoses made by RI pathologists, except for the **numerical magnitude** of lymphoma responses
 - ✓ Issue is **quantitative, not qualitative**
- ✓ US EPA uses RI solid-tumor data

Rare Kidney Tumors: Highly Significant

- ✓ Transitional-cell carcinomas of renal pelvis/ureter are **highly significant** and **extremely rare** in controls.
 - ✓ In 17 studies they were found in **2/2,669** control S-D rats (Toxicol Pathol 1991;19(3):27-9)
- ✓ They were found in **21/1500** aspartame treated S-D rats, versus **none in controls**.
- ✓ Chemical-induced rarely occurring kidney tumors are considered **clear evidence of carcinogenicity**.

Does Infection, Not Aspartame, Explain Lymphomas/Leukemias? **NO**

See:

Caldwell JC et al., "Evaluation of Evidence for Infection as a Mode of Action for Induction of Rat Lymphoma," *Env. & Molecular Mutagenesis* 49: 155-164, 2008

Caldwell JC et al., "Response to Letters to the Editor: Caldwell et al. [2008]," *Env. & Molecular Mutagenesis* 50:6-9, 2009

Gift et al. *Environ Health Perspect* 2013; 121:1253-1263.

Do Studies That Did Not Find Cancer Outweigh Studies That Did? **No**

- ✓ Industry studies: fail to meet 50 animals/sex/dose (used 36-40)
VS. RI studies (62-150 animals/sex/dose)
- ✓ NTP transgenic studies: no longer used for cancer evaluation screening; considered not reliable
- ✓ Lim study: Aspartame wasn't approved until subjects were in their late 30s/40s/50s or older. **Exposures early in life are likely to be much more critical. Only five year follow-up.** Other major weaknesses

EFSA Analysis Flawed

- ✓ Sharply Criticized for Bias and Conflicts of Interest
- ✓ Cut-and-Pasted from Industry Review
- ✓ Overlooked Weaknesses of Negative Studies
- ✓ Dismissed Strengths of Positive Studies
- ✓ Used historical control data in a biased and inappropriate way (as per IARC)

Conclusion: Designate Aspartame Highest Priority

- ✓ Widely consumed; early life exposures
- ✓ Positive in three well-designed and executed animal studies
 - ✓ In utero exposure and post-natal exposures throughout lifetime
 - ✓ Cancers in both genders
 - ✓ Multiple sites of cancer
- ✓ Supportive evidence from one human study
- ✓ Negative studies underpowered, lack sensitivity to detect cancers

Extra Slides

High Consumer Exposure

- ✓ One of most widely consumed artificial sweeteners
- ✓ Primary source of exposure is diet soda; in many of the biggest brands of diet soda (e.g., Diet Coke/Pepsi)
- ✓ Also tabletop sweeteners, desserts, candy, gum, and other foods, plus drugs, vitamins, toothpaste

Aspartame Causes Multiple Cancers

- ✓ *Lymphomas/leukemias* in rats (both sexes), 2 studies
- ✓ *Transitional-cell carcinomas of renal pelvis/ureter* in female rats
- ✓ *Malignant schwannomas* in male rats
- ✓ *Mammary cancers* in female rats after perinatal-through-adult exposure
- ✓ *Hepatocellular and alveolar/bronchioloar carcinomas* in male mice after perinatal-through-adult exposure

Ramazzini: What is the Evidence? (Continued)

- ✓ well-organized, clean facility"
- ✓ " apply **meticulous detail** to the necropsy and to the recording, collecting, and archiving of materials and tissues."
- ✓ Histologic quality of the sections "**very good**" said QA pathologist, with "**no deficiencies** that interfered with the examination or the interpretation of histopathologic changes that were present"
- ✓ "neither the occasional cases with tissue autolysis nor the use of alcohol fixation presented diagnostic difficulties"

Are Ramazzini Institute Tumor Diagnoses Reliable? **YES**

- ✓ QA pathologists for the PWG and the PWG itself agreed with diagnoses made by RI pathologists, except for the *numerical magnitude* of lymphoma responses
- ✓ For MTBE, only “a few” of the original (RI) diagnoses of lymphoma/leukemia were *not* confirmed by the QA pathologist. The PWG found lymphomas in female rats, although fewer than RI or QA pathologists.

Does Infection, Not Aspartame, Explain Lymphomas/Leukemias? **NO**

- ✓ Since respiratory infections occur in old rats, and in most RI bioassays, but leukemia/lymphoma are only reported in a few (8/112) RI bioassays, the link is unlikely
- ✓ In studies of ethylene and propylene oxide, *M. pulmonis* infection affected survival, yet lymphomas/leukemias were not increased

Caldwell JC et al., "Evaluation of Evidence for Infection as a Mode of Action for Induction of Rat Lymphoma," *Env. & Molecular Mutagenesis* 49: 155-164, 2008

Caldwell JC et al., "Response to Letters to the Editor: Caldwell et al. [2008]," *Env. & Molecular Mutagenesis* 50:6-9, 2009

Kidney Tumors - Continued

- ✓ Carcinomas in females: positive trend ($p < 0.05$), and significant increase ($p < 0.05$) in high dose females
- ✓ Furthermore, statistically significant increases of dysplastic lesions + carcinomas of renal pelvis/ureter were seen in the four top doses, with a positive trend in females ($p < 0.01$).
- ✓ “The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed.” (IARC)

Does Infection, Not Aspartame, Explain Lymphomas/Leukemias? **NO**

- ✓ Lymphoma/leukemia in two aspartame studies
- ✓ Positive significant trend in males and females, significant increase in females at 5 doses (first study)
- ✓ Significant d-r increase in females, especially high dose ($p < 0.01$) and in high dose males (second study)
- ✓ Controversy is quantitative, not qualitative
- ✓ All animals were housed in the same room (personal communication, M. Soffriti)

Do Studies That Did Not Find Cancer Outweigh Studies That Did? **No**

- ✓ To conclude lack of carcinogenicity, IARC requires multiple, mutually consistent, adequately powered studies covering the full range of human exposures that exclude with reasonable certainty bias, confounding, and chance and provide individual and pooled estimates of risk near unity with narrow confidence intervals.
- ✓ For cancer studies in humans, “latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity” (IARC)

Evidence for Carcinogenicity

IARC: “The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) **two or more species of animals** or (b) **two or more independent studies in one species carried out at different times** or in different laboratories **or under different protocols.**”

EFSA Analysis: Flawed

“It is generally **not appropriate** to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls” (IARC Preamble)

“The ANS Panel ... and EFSA ... concluded that the hepatic and pulmonary tumour incidencesall fall within their own historical control ranges ... Based on these data, the Panel concluded that the results ... do not provide evidence for a carcinogenic effect of aspartame in mice.”