# Comments to the
# Proposition 65 Carcinogen Identification Committee

## Aspartame

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Submitted by:

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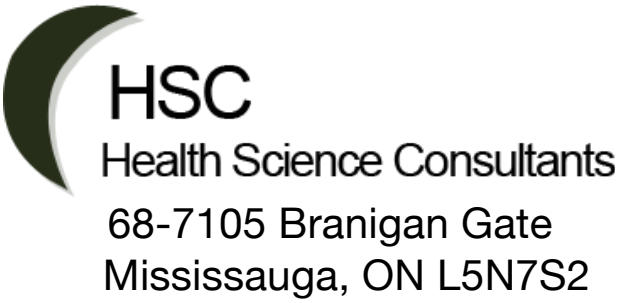

**Introduction:**
I am writing with regard to your upcoming Carcinogen Identification Committee (CIC) meeting o November 15, 2016 that will prioritize several chemicals, including aspartame for possible preparation of hazard identification materials. I am food toxicologist, with advanced degrees in food science, nutrition and toxicology, recognized Fellow of the Academy of Toxicological Sciences, and have over 25 years of experience in chemical food safety assessment. My PhD research was on chemical carcinogenesis and my post-doctoral training was in biochemistry and pathology. I have been examining the literature on aspartame, aspartame metabolism, consumption and safety assessments since 1995 when I became a faculty member at the University of Idaho and was responsible for outreach to the public on the safety of food ingredients and contaminant chemicals. I chaired an international expert committee review of the safety of aspartame, whose report was published in Critical Reviews of Toxicology in 2007.

**Summary:**
I recommend that the CIC maintain or lower aspartame's current priority level, which is "at the bottom of the medium category." Aspartame's priority level should not be elevated based on the current science, which i not accurately reflected in the information in the recent Office of Environmental Health Hazard Assessment (OEHHA) notice a explained below.

**Epidemiological data:**
The findings an conclusions of the study by McCullough *et al* (2016 are not accurately represented in the Aug 201 Office of Environmental Health Hazard Assessment (OEHHA) notice. McCullough and colleagues (2016 reported that when males and female subjects were combined, consumption of aspartame from low calorie sodas was **not** positively associated with risk of overall NHL nor with any major subtypes, but rather demonstrated a trend of reduced ris of multiple myeloma, although not statistically significant (RR: 0.70; 95% CI: 0.42, 1.17 for 1.78 L or cans soda/wk vs none; P-trend: 0.05). When men and women were analyzed separately, additional evidence for negative associations of consumption of aspartame from low calorie sodas and overall NHL in women were observed (P = 0.03). This appeared to be the result of an inverse association with multiple myeloma (RR: 0.50; 95% CI: 0.20, 1.26; P-trend: 0.04) in addition to other nonsignificant inverse associations for NHL subtypes (P-trend: 0.10–0.43). Furthermore, in women, long-term regular consumption of aspartame from low calorie sodas was associated with a lower NHL risk (RR: 0.53; 95% CI: 0.32, 0.87), compared with long-term nondrinkers.

The statement presented by the OEHHA that "*Increased risks observed for all non-Hodgkin lymphoma (including multiple myeloma)" (*based on data in Table 4 in McCullough *e al*., 2016) i misleading. The OEHHA fails to report that the RR for each of the categories and subtypes, although slightly higher in the first quintile of consumers compared with non-consumers, actually decreased with increased consumption of aspartame for every category and every subtype *including multiple myeloma and diffuse large B-cell lymphoma,* clearly demonstrating that risks were NOT increased with aspartame consumption.

In addition to the epidemiological studies described by OEHHA, (Lim *e al.* (2006); Schernhammer *et al.* (2012); McCullough *et al.* (2014); Gurney *et al.* (1997); Gallus *e al.* (2007 and Cabaniols *e al.* (2011), the following epidemiological studies on aspartame and cancer risk have also been published. These case control and cohort studies provide additional support for the lac of positive association between aspartame consumption and cancer risk. These are summarized in the attached Table.

(1 Ewertz and Gill (1990), case control for breast cancer,
(2 Hardell *et al* (2001) case control for brain cancer.
(3 Bunin *et al* (2005 case control for childhood brain cancer
(4 Bao *e al* (2008 cohort, pancreatic cancer
(5 Bosetti *et al* (2009 case control, various cancers (stomach, pancreas, and endometrium)
( Chan *et al* (2009) cas control, Northern California, pancreatic cancer

**Animal carcinogenicity data:**

The summary in the OHEEA notice is incorrect. There have not been additional studies published since 2009; there has only been one (Soffritti *et al*. 2010) All the other studies mentioned in the OEHHA notice were published in the literature or described in expert panel and regulatory reviews of aspartame prior to 2009 The reported results by OEHHA of several studies also need to be addressed.

Firstly, the conclusion of the two-year studies in male and female Charles River Caesarean Derived (CD) Sprague-Dawley rats: Searle Laboratories (1973) was "no treatment related tumor findings" following extensive re-evaluation of brain tissues. This was also the conclusion of every independent regulatory agency that peer-reviewed the study prior to approval of aspartame (reviewed in EFSA 2009, Magnuson *et al*., 2007)

Secondly, the results for the 3 studies reported Soffritti *e al* (2006, 2007, 2010) of the Ramazzini Institute (RI) as described in the OEHHA notice are those of the authors, but numerous independent reviewers of these studies disagree with the authors' conclusions and find that the RI studies provide no evidence of carcinogenic potential of aspartame.

Due to increasing evidence of discordance of the conclusions of the carcinogenicity studies conducted by the RI and those conducted by other laboratories for variety of compounds, extensive reassessment of the validity of RI studies ha been undertaken by various authors an government agencies (Cruzan, 2009; Gift *e al*., 2013; EFSA 2009, EFSA 2013; Magnuson *et al*., 2007, EPA 2011, FDA 2007, and the National Toxicology Program, 2011). A detailed discussion of the shortcomings and problems with the RI studies is not appropriate at this time but has been extensively documented (Cruzan, 2009; Gift *et al*., 2013; EFSA 2009, EFSA 2013; Magnuson *e al*., 2007, EPA 2011, NTP 2011). The conclusion of every review has been the same: the carcinogenicity studies conducted by the RI are flawed, are confounded by high incidence of disease, and the pathological findings and conclusions are unreliable. The critical point is that the studies reported Soffritti *e al* (2006, 2007, 2010) DO NOT provide credible evidence of carcinogenic ris from human consumption of aspartame-containing foods and beverages.

**Other relevant data:**
The OEHHA notice also misrepresents the findings by the Expert Panel report by Magnuson (Magnuson *et al.,* 2007 regarding the metabolism of the aspartame digestion product, methanol, to formaldehyde as a potential carcinogenic mechanism. The published conclusions of the Expert Panel were " *Therefore, it is highly unlikely that formaldehyde formed from the small amount of methanol from consumption of aspartame poses an carcinogenic risk to humans."* (Magnuson *et al*., 2007). This was also the conclusion reached by the EFSA 2013 aspartame review panel. Using current consumption databases, EFS estimated that the amount of methanol exposure resulting from the highest consumption of aspartame is less than 10% of the total daily human methanol exposure when considering both endogenous and exogenous sources.

EFSA further discussed the uncertainty of the carcinogenic potential of methanol itself, as the RI methanol study has been reevaluated and criticized by several groups including an NTP pathology working group (Cruzan, 2009; Schoeb *e al*., 2009; Schoeb and McConnell, 2011; NTP, 2011) Therefore, there i no credible scientific evidence that human consumption level of aspartame generate

sufficient metabolites to pose a carcinogenic risk to humans.

**Reviews:**
In addition to the EFSA 2013 review, Kirkland and Gatehouse (2015) published a review of the genotoxicity studies for aspartame and concluded "***T****he available data therefore support the conclusions of the European Food Safety Authority (EFSA) that aspartame i  non-genotoxic*".

**Conclusion:**
Since 2009, the evidence for the **lack** of carcinogenic potential of aspartame has increased. Aspartame's priority level should be either lowered or remain the same.

**References:**


Bao, Y., Stolzenberg-Solomon, R., Jiao, L., Silverman, D.T., Subar, A.F., Park, Y., Leitzmann, M.F., Hollenbeck, A., Schatzkin, A., Michaud, D.S., 2008. Added sugar and sugar-sweetened foods and beverages and the risk of pancreatic cancer in the National Institutes of Health-AARP Diet and Health Study. Am. J. Clin. Nutr. 88, 431–440.

Bosetti, C., Gallus, S., Talamini, R., Montella, M., Franceschi, S., Negri, E., La Vecchia, C., 2009. Artificial sweeteners and the risk of gastric, pancreatic, and endometrial cancers in Italy. Cancer Epidemiol. Biomarkers Prev. 18, 2235– 2238.

Bunin, G.R., Kushi, L.H., Gallagher, P.R., Rorke-Adams, L.B., McBride, M.L., Cnaan, A., 2005. Maternal diet during pregnancy and its association with medulloblastoma in children: a children's oncology group study (United States). Cancer Causes Control 16, 877–891.

Cabaniols C, Giorgi R, Chinot O, Ferahta N, Spinelli V, Alla P, Barrie M, Lehucher-Michel MP. Links between private habits, psychological stress and brain cancer: a case-control pilot study in France. J Neurooncol. 2011 Jun;103(2):307-16.

Chan, J.M., Wang, F., Holly, E.A., 2009. Sweets, sweetened beverages, and risk of pancreatic cancer in a large population-based case-control study. Cancer Causes Control 20, 835–846.

Cruzan G. 2009. Assessment of the cancer potential of methanol. Crit Rev Toxicol 39(4):347–363.

EFSA. Report of the meeting on Aspartame with National Experts. 2009. https://www.efsa.europa.eu/en/supporting/pub/1641

EFSA. Scientific opinion on the re-evaluation of aspartame (E951) as a food additive. EFSA Journal. 2013, 11 (12) 3496 (263pp).

Ewertz, M., Gill, C., 1990. Dietary factors and breast-cancer risk in Denmark. Int. J.Cancer. 46, 779–784.

FDA CFSAN/Office of Food Additive Safety Statement on European Aspartame Study, http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm208580.htm. April 2007.

Gift JS, Caldwell JC, Jinot J, Evans MV, Cote I, Vandenberg JJ. 2013. Scientific considerations for evaluating cancer bioassays conducted by the Ramazzini Institute. Environ Health Perspect. Nov-Dec;121(11-12):1253-63.

Hardell L, Mild KH, Påhlson A, Hallquist A. Ionizing radiation, cellular telephones and the risk for brain tumours. Eur J Cancer Prev. 2001 Dec;10(6):523-9.

Kirkland D and Gatehouse D: Aspartame: a review of genotoxic data. Food and chemical toxicology, 84, 161-168, 2015.

Magnuson BA, Burdock GA, Doull J, Kroes RM, Marsh GM, Pariza MW, Spencer PS, Waddell WJ, Walker R, Williams GM. Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. Crit Rev Toxicol. 2007;37(8):629727.

NTP (National Toxicology Program). 2011. Summary Report of the National Toxicology Program and Environmental Protection Agency Sponsored Review of Pathology Materials from Selected Ramazzini Institute Rodent Cancer Bioassays. Research Triangle Park, NC:NTP. Available: http://ntp.niehs.nih.gov/NTP/About_NTP/Partnerships/International/SummaryPWG_Report_RI_Bioassays.pdf.

Schoeb TR, McConnell EE, Juliana MM, Davis JK, Davidson MK and Lindsey JR: Commentary – Mycoplasma pulmonis and lymphoma in bioassays in rats. Vet. Pathol., 46, 952-959, 2009.

Schoeb TR and E.E. McConnell EE: Mycoplasma pulmonis and lymphoma in a methanol bioassay. Vet. Pathology, April 2011.

Schoeb TR and E.E. McConnell EE: Further comments on Mycoplasma pulmonis and lymphoma in bioassays of rats. Vet. Pathology 48 (2) 420-426, 2011.

Soffritti M, Belpoggi F, Manservigi M, Tibald E. Aspartame administered in feed, beginning prenatally through life span, induces cancers of the liver and lung in male Swiss mice. American J. of Industrial Medicine, 53, 1197-1206, 2010.

U.S. EPA (U.S. Environmental Protection Agency). 2012. Update on Ramazzini Institute Data in IRIS Assessments. Washington, DC:U.S. EPA. Available: http://epa.gov/iris/ramazzini.htm .

| Author | Type of study (N) | Consumption | Conclusions |
|---|---|---|---|
| Ewertz and Gill, 1990 | Case-control; Denmark<br>1,336 women, breast cancer risk | Artificial sweeteners | **No association with cancer risk**<br>**(OR=0.94, 95% CI 0.73-1.20 for use versus non-use)** |
| Hardell (2001) | 3 brain tumor cases<br>4 controls | Recall of low-calorie soft drinks. | **No association with cancer risk** |
| Bunin (2005) | 31 child brain tumor cases,<br>31 controls | Food frequency by mothers | **No association with cancer risk** |
| Bao et al., 2008 | Cohort; NIH-AARP Diet and Health Study<br>1,258 cases of pancreatic cancer. | Diet soft drinks | **No association with cancer risk**<br><br>R of 1.11 (95% CI 0.86-1.44) highest quintile of consumption versus never drinkers |
| Bosetti (2009) | Case control; various cancers (1010 cases, 2107 controls) stomach, pancreas and endometrium, | Food frequency questionnaires | **No association with cancer risk** |
| Chan et al., 2009 | Case control, Northern California<br>53 pancreatic cancer cases | Food frequency questionnaires | **No clear association with aspartame consumption.**<br>Increase risk for low cal cola, OR=1.7, 95% CI 1.2-2.4, for ≥1/day versus non-drinkers, BUT not for low cal caffeine free cola or other low cal beverage |