EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) Consultation
Draft scientific opinion on the re-evaluation of aspartame as a food additive

Comments submitted by Center for Science in the Public Interest,
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KEY:
EFSA: European Food Safety Authority
ERF: European Ramazzini Foundation
IARC: International Agency for Research on Cancer
MPL: Maximum Permitted Level
NTP: National Toxicology Program
Searle: G. D. Searle, the manufacturer and patent owner of aspartame
PWG: Pathology Working Group, organized by the National Toxicology Program

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1. INTRODUCTION

These comments are submitted on behalf of the Center for Science in the Public Interest as well as of Kathleen Burns, PhD, Director, Sciencecorps, James Huff, PhD, Guest Researcher,
National Institute of Environmental Health Sciences (for affiliation purposes only), and Ronald Melnick, PhD of Ron Melnick Consulting LLC.

Scientific concerns beyond those noted in these comments remain, but are not addressed due to time constraints.

3. BIOLOGICAL AND TOXICOLOGICAL DATA OF ASPARTAME

Lines 1331-1334: Three key peer reviewed papers should be added:

2) J. C. Caldwell et al, “Response to Letters to the Editor: Caldwell et al. [2008],” Env. & Molecular Mutagenesis 50:6-9, 2009

Those sources should end criticisms of the ERF program and clarify the significance of the ERF findings.

The focus of [1] addresses the invalidity of EFSA Panel’s hypothesis that infection in ERF rats, not aspartame, caused lymphomas/leukemias in Soffritti’s 2006 study. We find the arguments in [1,2] scientifically compelling. For example, if respiratory infections occur in most ERF bioassays, but leukemia/lymphoma only reported for a few, the link between them is unconvincing. Also, Caldwell cites bioassays of propylene oxide and ethylene oxide in F344 rats that found M. pulmonis infection not related to chemical exposure, but affected survival, yet lymphomas/leukemias were not increased.

The PWG reports [3] add important detail to the Summary Report of the NTP-/EPA-Sponsored Review (Nov. 29, 2011), together comprising the most comprehensive review of ERF laboratory practices and pathology evaluations available. The PWG declared ERF 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.” [3] documents 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.” In fact, NTP and ERF are the two largest and most well-established bioassay programs in the world, and a comparative review found remarkably consistent results (Huff, Ann N Y Acad Sci. 2002 Dec;982:208-30.)
Significantly, QA pathologists of the PWG and the PWG itself agreed with diagnoses made by ERF pathologists, except for the numerical magnitude of lymphoma responses. For example, for MTBE, the PWG report states that only "a few" of the original diagnoses of lymphoma/leukemia were not confirmed by the QA pathologist, and the PWG also confirmed some lymphomas [in female rats, 0 (controls), 1 (low dose), and 4 (high dose)], although fewer than ERF or QA pathologists. Also, a 2004 PWG Report of the ERF study that focused specifically on aspartame, cited in [1] and obtained under the Freedom of Information Act, states “The diagnoses of lymphatic and histocytic neoplasms in the cases reviewed were generally confirmed.”

**Lines 1335-1343:** Most long-term toxicity studies supporting approval of aspartame, noted here, are old, unpublished, and do not meet current protocol or scientific standards. In particular, most used small numbers of animals and lack statistical power. For example, Searle’s long-term studies used 36-40 animals/sex/group (60-72 controls/sex), or 280-440 animals per study, reporting few if any adverse effects. In contrast, the 2006 ERF bioassay used 100-150 animals/sex/group, equaling 1,800 animals, and reported multiple adverse effects including cancers, as did two later ERF bioassays including in utero exposures. Of course the age of studies should not per se be used to disqualify them, if designs, conduct, and reporting were appropriate. However, these older industry studies must be considered inadequate to detect effects that occur at low incidences.

3.2.4.2 ADDITIONAL LONG-TERM CARCINOGENICITY STUDIES

Our comments in sections 3 and 4 apply here too.

Cancers other than lymphomas/leukemias in ERF aspartame bioassays include transitional-cell carcinomas of renal pelvis/ureter in female rats, malignant schwannomas in male rats, and mammary cancers in female rats and hepatocellular carcinomas and alveolar/bronchiolar carcinomas in male mice after perinatal through adult exposure.

Diagnoses of these cancers are not at issue: PWG QA pathologists largely agreed with diagnoses made by ERF pathologists, except for some lymphomas, and EPA stated it will continue to consider ERF solid-tumor data in its assessments (http://www.epa.gov/iris/ramazzini.htm). Using IARC and EPA criteria, these results – three studies, two species, both genders, and multiple sites -- show unequivocal evidence aspartame is carcinogenic in animals, and possibly or probably carcinogenic in humans.

Since the first ERF rat study was comparatively large (1,800 animals), used a wider range of doses, and did not begin in utero, as did the second ERF rat study, exactly consistent results from both studies should not be expected. Yet, the ESFA Panel cites lack of consistency as a reason to discount ERF’s results. For example, in the first study, 3/150 (2%) of females had carcinomas of renal pelvis/ureter at 100 mg/kg. Since the second rat study used only 70 rats/sex/group, the same 2% rate would have only 1 animal with this
carcinoma at 100 mg/kg. Also, different exposure scenarios produce different cancer patterns. For example, daughters exposed to DES before birth have greater risks of cervical/vaginal cancer, while mothers have a higher risk of breast cancer.

Transitional-cell carcinomas of renal pelvis/ureter are highly significant and extremely rare in controls. They were only found in one male and one female Sprague-Dawley rats of 2,669 controls in 17 studies, and in one male F-344 rat of 1,060 controls in 10 studies. (Toxicol Pathol. 1991;19(3):287-9; http://tpx.sagepub.com/content/19/3/287.long). Aspartame-treated animals had 21 transitional-cell kidney carcinomas vs none in controls. Statistically significant increases of dysplastic lesions and carcinomas of the renal pelvis/ureter were seen in the four top doses, with a positive trend in females. IARC states “The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed.” Chemical-induced rarely occurring kidney tumors are considered clear evidence of carcinogenicity.

The NTP PWG on the first ERF rat study wrote “cases diagnosed as malignant schwannoma of the cranial nerve were generally confirmed by the PWG,” although some members “preferred a diagnosis of sarcoma, NOS [not otherwise specified]”, both evidence of carcinogenicity.

As IARC states “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 …” Yet this is what the ESFA Panel has done.

The notion that there was no “formal” quality assessment process for pathology diagnoses should not disqualify ERF results. There is no mention of this criterion being applied to Searle studies.

**Lines 2369-2373**: Add NTP’s conclusion [2005 report]: “Because this is a new model, there is uncertainty whether the study possessed sufficient sensitivity to detect a carcinogenic effect”. In fact, these studies were predicted to be negative, as the transgenic models are not considered to be reliable for cancer evaluations. NTP no longer uses them for screening potential carcinogens. Hence negative findings in this model are not evidence that aspartame does not cause cancer.

**3.2.7.1.2 EPIDEMIOLOGICAL STUDIES OF ASPARTAME AND CANCER**

**Lines 3190-3194**: The Panel highlights “major strengths” of the Lim 2006 study, but neglects several significant weaknesses. Their study only evaluated short-term exposures in older adults [50-71 years]. Exposures early in life are likely to be much more critical. “Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens” (US EPA, 2005) provides examples and information on why one would not expect the same cancer responses from in utero and adult exposure. The exposure period was likely less than 10 or 15 years, given the timing of the surveys and commercialization
of aspartame. Consumption estimates were based on self-recall of beverage consumption during a 12-month period. Exposure thus is poorly characterized. The magnitude of the exposure was not great (only 4% of subjects were in the highest exposure group, equivalent to ~3.3 12 ounce cans of diet soda/day). A five-year follow-up is also too short to allow firm conclusions. 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. In addition, IARC cautions that “latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.” Ergo, the non-positive finding provides little reassurance of an absence of cancer hazard.

**Lines 3202-3227** It is noteworthy that the tumor type in this study is the same as found in two rat studies of aspartame, adding credence that aspartame plays a role in inducing lymphomas/leukemias.

**Lines 3228-3229** For balance, the report should state, “Overall, the Panel considered the results of these epidemiological studies do not suggest an increased risk associated with aspartame consumption for the types of cancer examined, nor do they provide reliable evidence of non-carcinogenicity of aspartame.”

4. DISCUSSION OF ASPARTAME TOXICITY DATABASE

Because ERF studies are carried out until natural death of animals, it should not be surprising that some exhibited bronchitis, symptoms of infection, or other changes associated with ageing/dying; this should not distract from or diminish the significance of aspartame-induced cancer findings, as the commentary by Schoeb and McConnell suggests. The only issue concerns diagnosis of lymphomas in the lung. We support the use of lifetime studies, since some cancers take longer to develop and would be missed by terminating at 104 weeks [Environ Health Perspect. 2008 Nov;116(11):1439-42]. This study protocol (i.e., lifespan studies) has been credited as the primary reason ERF was the first laboratory to associate carcinogenic responses with chemicals that are now recognized as known human carcinogens, such as vinyl chloride and benzene.

Most studies have flaws, particularly older ones; for example, the Searle long-term studies fail to meet current standards for numbers of animals, and thus lack statistical power. The Panel overlooks these and other flaws, yet finds ways to ignore multiple cancers in three studies and two species, from a program whose procedures and results have been carefully scrutinized and found to produce reliable results. The Preamble to IARC Monographs states, “Sufficient evidence of carcinogenicity: 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.” We are dissatisfied with the cursory evaluation of the ERF studies, reliance on former evaluations, failure to consider sources cited in our previous comment, lack of consideration of tumors other than lymphomas/leukemias, and in general, lack of probing analyses of the ERF results.

5.2.5 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY OF METHANOL

We note that other authorities consider methanol to be a chemical with reproductive/developmental concerns. For example, the State of California listed methanol as a chemical known to the state to cause reproductive toxicity, based on developmental toxicity effects identified by NTP. We remind the Panel of errors in 2.8.4.4 that characterize exposure to methanol. Given all this, and that there is individual variation in metabolic processes, and that pregnant women likely consume larger-than-anticipated amounts of artificial sweeteners, since they consume more fluids than women who are not pregnant and because pregnant women may seek to limit weight gain through use of artificial sweeteners, we are not convinced that the amount of methanol released from aspartame does not pose a developmental toxicity concern.

2.6.1.2 SUMMARISED DATA ON REPORTED USE LEVELS IN FOODS FROM INDUSTRIES AND OTHER SOURCES

Page 30, TABLE 6, after line 811, 5.3.1 – Chewing gum with added sugar:

The level used for calculation is only 58% of the MPL [maximum permitted level]. This value was chosen solely on the basis of data provided by the International Chewing Gum Association. The comment is made that “Maximum levels up to 7% of chewing-gums and 50% of chewing-gum contains aspartame as flavor enhancer at a typical level.” Consumers may be exposed to the MPL in some chewing gums. The level used for calculation should be the MPL, not 58%.

Page 31, TABLE 6, after line 811, 14.1.3 – Fruit nectars as defined by Council Directive 2001/112/EC and vegetable nectars and similar products:

The MPL is eight times higher than the Level used for calculation, which is based on data from only one country (Austria). Consideration could be given to lowering the MPL, but meanwhile, the existing MPL should be used for calculation. This is particularly important since this category is one of the largest contributors to exposure from aspartame for toddlers and children.

Page 32, TABLE 6, after line 811, 17 – Food supplements as defined in Directive 2002/46/EC excluding food supplements for infants and young children.
The level used for calculation is only about 40% of the MPL, and this is based on data from two countries (n=3 and n=17). This category is very diverse and the data provided may not be representative. The MPL should be used so as not to underestimate exposure.

2.8.4.4 COMBINED EXPOSURE TO METHANOL FROM ENDOGENOUS AND EXOGENOUS SOURCES

Page 45 Table appearing after line 1201: The figures in the table need correcting. For example, the exposure range from methanol from all endogenous pathways and natural food occurrence is lower than the total anticipated exposure to methanol from all sources (endogenous pathways, natural food occurrence, and aspartame as a food additive) for high-level exposed children.