Consideration of the Prioritization of Aspartame

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I am writing concerning the California Proposition 65 Carcinogen Identification Committee (CIC) prioritization of aspartame. I strongly recommend that CIC maintain aspartame's current priority level of, "at the bottom of the medium category". It would be highly inappropriate to classify aspartame as having any possible carcinogenic activity.

I have extensive experience in human pathology, experimental pathology, carcinogenicity testing, and risk assessment. I have been a member of the International Programme on Chemical Safety (IPCS) committee that has been involved with the development of the mode of action and human relevance framework, have been a member of the Board of Scientific Counselors of the National Toxicology Program (NTP) and the Board of Scientific Counselors of the National Institute of Environmental Health Sciences (NIEHS), in addition to serving on numerous other committees and panels for the FDA, EPA, NAS, and NIH in the United States. I have published extensively on various aspects of pathology, toxicology, carcinogenesis, and risk assessment. Furthermore, I am a member of the expert panel of the Flavor and Extract Manufacturer's Association (FEMA) that reviews the "Generally Recognized As Safe" (GRAS) status of flavor ingredients. I have received numerous awards for my efforts in research, including the Arnold J. Lehman Award from the Society of Toxicology, the Lifetime Achievement Award from the Society of Toxicologic Pathology, and I will receive the Distinguished Scientist Award from the American College of Toxicology in November, 2016.

The epidemiologic data does not support evidence of a carcinogenic potential in humans. In addition, the animal data are not supportive of carcinogenic activity in rats or mice. Since my area of expertise is primarily in evaluation of the animal studies and extrapolation to humans, I will focus my comments on those studies.

Most of the carcinogenicity studies of aspartame have been conducted in rats and mice and have been negative. These include three studies in mice by the National Toxicology Program (NTP). The NTP provides a rigorous evaluation of chronic toxicity and carcinogenic activity in rats and mice utilizing standardized procedures that have been developed and verified by them over the course of nearly five decades. These studies are extensively investigated with standardized protocols and with extensive pathology review. The NTP studies did not find any evidence of carcinogenic activity in mice, although these were shorter term studies than the standard 18 or 24 months studies usually performed, and they involved three different strains.
of genetically modified mice with specific sensitivity to lymphomas, brain tumors and skin tumors. The most definitive two year bioassays were studies performed in rats and mice by the original developer of aspartame, Searle, and these showed no evidence of carcinogenic activity in either species. These were performed as part of the regulatory submission regarding aspartame, and include a so-called 2 generation study in rats involving exposure in utero, during lactation, and continuing after weaning for 2 years.

The only suggestion of positive carcinogenicity findings in rats or mice have been reported by Soffritti et al., (2006, 2007, 2010) from the Ramazzini Institute in Italy. However, these studies are seriously flawed and they are not acceptable for evaluation of carcinogenic activity nor for the performance of a risk assessment for humans. There are several significant concerns from the studies at the Ramazzini Institute. To begin with, the studies utilize a non-standard protocol including lifetime administration of the chemical rather than the standard two-year bioassay. The difficulty with these studies is that the animals are allowed to die, which frequently leads to severe autolysis and difficulty in performing an adequate histopathologic evaluation. In addition, these animals are severely infected (they are not specific pathogen free, SPF) and frequently (nearly always) have pneumonia. This further complicates evaluation of carcinogenic activity since the presence of pneumonia in rodents, particularly mice, can be associated with the development of lymphoproliferative neoplasms (leukemia/lymphoma) even in untreated controls. These neoplasms are related to the infection and associated inflammation rather than due to the chemical. Furthermore, the Ramazzini Institute has until recently excluded peer review of the histopathology, a procedure that is standard practice in most centers performing bioassays and usually included in the evaluation of the carcinogenic activity of chemicals. The use of pathology peer review is routinely performed by the NTP and most other testing organizations. Recently, a peer review was permitted by the Ramazzini Institute of some of their studies, and the peer review team found serious difficulties in the interpretation of the pathology of their studies. These included the difficulty of diagnosis in the face of bronchopneumonia, significant errors in diagnosis, and inadequate training of the pathologist. The peer reviewers were not able to substantiate any of the conclusions of carcinogenic activity in the studies that they evaluated.

The inadequacies of the studies from the Ramazzini Institute are well known to regulatory authorities and have led them to not consider the results from the studies from the Ramazzini Institute in their overall risk assessment because of the serious flaws involved.

The reliability of the original regulatory required studies in rats and mice on aspartame should be the priority studies in the risk assessment of aspartame. The NTP studies are more focused for specific effects and support the conclusion of non-carcinogenicity of aspartame. The studies from the Ramazzini Institute should not be included in the review because of their fatal flaws. Without the results of the Ramazzini Institute, there would be no evidence of carcinogenicity in animals. In addition, most of the evidence suggests that aspartame is not genotoxic. Furthermore, the epidemiology supports the conclusion of a lack of carcinogenic activity in humans.
Based on these findings, it is appropriate for the Proposition 65 Carcinogen Identification Committee to maintain its current priority level for aspartame, which is "at the bottom of the medium category."