Aspartame Should Receive
the Lowest Possible Priority
for Further Carcinogenicity Review

Comments of the Calorie Control Council
to the
California Carcinogen Identification Committee

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Submitted by

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I. Executive Summary

The Calorie Control Council (CCC) recommends that the Carcinogen Identification Committee (CIC) assign aspartame the lowest possible priority for further carcinogenicity review.

Aspartame is one of the most thoroughly tested food additives in history. Over 100 countries have approved its safety for use in foods. Aspartame should receive the lowest possible priority for further carcinogenicity review because:

- All three of the conventional two-year cancer studies in rats were negative,
- The one conventional two-year cancer study in mice was negative,
- Three National Toxicology Program (NTP) cancer studies in transgenic mice were negative,
- It is not genotoxic,
- No increased risk of cancer attributable to aspartame was identified in any analytical epidemiological study, including a large (n = 473,984) prospective cohort study (Lim et al., 2006), and
- Other health authorities have recently reviewed all the carcinogenicity data concerning aspartame and found no cause for concern.

Indeed, OEHHA assigned aspartame a “not high” cancer priority in 2004. Since then, NTP released final reports that three separate NTP carcinogenicity studies in transgenic mice showed no link to cancer, and a well-conducted epidemiological study showing no association between cancer and aspartame consumption in humans (Lim et al. 2006) was published.

The only reports published since OEHHA’s 2004 prioritization review that assert evidence of carcinogenicity (combined leukemia/lymphoma) are two unconventional, flawed rat carcinogenicity studies (Soffritti et al., 2005; 2007) conducted by the European Ramazzini Foundation (the Ramazzini studies). These studies have been reviewed by expert groups such as the European Food Safety Authority (EFSA), the U.S. Food and Drug Administration (FDA), and a distinguished group of independent cancer specialists, and all have found that the Ramazzini studies should receive no weight in assessing evidence of carcinogenicity. For example, the EFSA recently reviewed all the available evidence on the potential carcinogenicity of aspartame, including the Ramazzini studies, and concluded in March 2009 that “there is no indication of any genotoxic or carcinogenic potential of aspartame.”

The Ramazzini studies have been discounted as without value by independent reviewers because of many serious problems with experimental design, interpretation of results and data reporting. For example, the studies’ rats (an inbred strain unique to this laboratory)

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were housed under substandard conditions, more than two-thirds suffered from bronchopneumonia, were allowed to live until spontaneous death (no scheduled sacrifice), and the study did not have an adequate pathology review (authors also refused to share all requested pathology slides with FDA and EFSA). In addition to the EFSA’s very recent critique of the Ramazzini studies, an independent expert panel of distinguished U.S. and European scientists made the following statement regarding the Ramazzini studies in a publication that OEHHA forwarded to the CIC:

“In summary, the [Ramazzini] reports alleging carcinogenicity are contradicted by many publications and every scientific consideration. Many potential flaws have been suggested in this [expert] report; . . . [I]t can be confidently stated that these [Ramazzini] reports provide no credible evidence that aspartame is carcinogenic.”

FDA reported in 2007 that it had requested study data from the European Ramazzini Foundation (ERF), reviewed the data ERF provided, and “finds that it [the data] does not support ERF’s conclusion that aspartame is a carcinogen.”

There is no credible evidence of carcinogenicity in humans. The single ecological study that reported an increase in brain tumors coinciding with the introduction of aspartame in foods did not even measure consumption, and represents a classic example of the “ecological fallacy.” This study has been widely questioned and criticized by many scientists. Subsequently, many well-conducted epidemiological (analytical) studies of aspartame have been conducted, and these studies reveal no link between cancer and aspartame consumption. For example, no increased risk of cancer attributable to aspartame was observed in a large (n = 473,984) prospective cohort study (Lim et al., 2006) and in an integrated analysis of several case-control studies of various cancers (Gallus et al., 2007).

Considering the scientific evidence, either in depth or by reviewing the summaries and abstracts, aspartame should receive the lowest priority for carcinogenicity review. The critical reviews by EFSA, FDA, the Expert Panel, the UK Committee on Carcinogenicity of Chemicals in Food, and Health Canada provide overwhelming support for assigning the lowest priority status of aspartame. Hazard materials should not be prepared for a chemical with no credible evidence of carcinogenicity. A CIC listing review would unnecessarily duplicate these consistent independent analyses of aspartame and would unnecessarily blemish the safety profile of aspartame by identifying it as presenting carcinogenic concern.

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2 Magnuson, et al., Aspartame: A Safety Evaluation Based on Current Use Levels, Regulations, and Toxicological and Epidemiological Studies, Critical Reviews in Toxicology 37: 629-727 at 669 (emphasis added) (referring to the first ERF study). A similar assessment of the second ERF study appears in the Magnuson et al. Addendum at pages 702-703: "In summary, considering the lack of significant differences between high dose groups and historical control cancer rates, plus the many deficits in the study design and data, it is the opinion of this expert panel that this study (Soffritti et al., 2007) fails to provide convincing evidence of aspartame carcinogenicity."

II. Introduction

Aspartame, a synthetic nonnutritive sweetener, has been approved for use in food in more than 100 countries, including the U.S., Canada, countries of the European Union (EU), Japan, and Australia.\(^4\) No country has declined to approve the use of aspartame in food. Neither aspartame nor its components accumulate in the body.

Aspartame is a very simple ingredient that is quickly broken down and not absorbed into the body intact. The gastrointestinal tract breaks aspartame down into three components: amino acids, aspartic acid (40% by weight) and phenylalanine (50% by weight), and methanol (10% by weight). These components are then absorbed and utilized by the body via the same metabolic pathways as when they are derived from common foods. Common foods, such as milk, fruits and vegetables, actually provide far greater amounts of aspartic acid, phenylalanine, and methanol than does aspartame in the diet. In fact, a serving of non-fat milk provides about 6 times more phenylalanine and 13 times more aspartic acid compared to an equivalent amount of diet beverage sweetened with aspartame. Likewise, a serving of tomato juice provides about 6 times more methanol compared to an equivalent amount of diet beverage with aspartame. Once broken down, aspartame’s components are absorbed into the blood and used in normal bodily processes, just as they would be when derived from other foods. In other words, aspartame should be an even lower priority for carcinogenicity review than common foods, such as milk and tomato juice.

OEHHA (i) performed a preliminary toxicological review of aspartame in 2002 and 2003, (ii) released a draft “not high” priority for aspartame in October 2003, (iii) received public comments on aspartame, (iv) held a public workshop on prioritization of aspartame and other chemicals in November 2003, and (v) finalized the “not high” priority in March 2004. A copy of the March 2004 final prioritization document for aspartame is attached to these comments for your reference.

In her April 3, 2009, letter to the CIC, Dr. Denton explained that OEHHA is interested in the CIC articulating a “high,” “medium,” “low,” or “no priority” recommendation for each of the 38 chemicals for which the CIC received data from OEHHA.

The CIC should recommend that aspartame receive the lowest possible priority for further review because FDA, an authoritative body, recently reviewed data on the potential carcinogenicity of aspartame and found no basis for concern, and because OEHHA’s own 2004 review of aspartame revealed that the chemical was a not high priority. The well conducted epidemiological studies, the four conventional two-year cancer bioassays in two different species, and the three NTP bioassays in transgenic mice all support this recommendation.

The prioritization process “is designed to ensure that the efforts of [the CIC] are focused on chemicals that may pose significant hazards to Californians.” Even on preliminary review of the data and commentary, aspartame does not pose a significant hazard to Californians and thus should not be advanced to listing evaluation by the CIC.

The following sections of this submission briefly summarize the available evidence of carcinogenicity of aspartame. We believe the scientific evidence regarding the potential carcinogenicity of aspartame supports the CIC assigning aspartame the lowest possible priority for further review. There is no credible evidence of carcinogenicity in either animals or humans.

III. OEHHA assigned aspartame a “not high” priority in 2004, and research reported since then is reassuring that aspartame is not carcinogenic.

In March of 2004, OEHHA stated that “aspartame did not reach a level of carcinogenicity concern sufficient to be placed on the candidate list [for CIC carcinogenicity review].” This evaluation was presented despite a modest concern over observations of brain tumors in aspartame-treated rats. Since the “not high” priority was finalized by OEHHA in 2004, the only new potential evidence of carcinogenicity is two unconventional, widely criticized and widely

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5 Process for Prioritizing Chemicals for Consideration Under Proposition 65 by the “State’s Qualified Experts,” page 1 (OEHHA, 2004).

6 OEHHA noted what it considered a statistically significant increase in brain tumor incidence based on initial data from the first rat carcinogenicity study (Searle, E33/34, 1973). Subsequently, the study authors performed a more thorough and extensive histopathological evaluation of the animals’ brains for the presence of tumors. In the original study, the investigators assessed two sections per brain; in the follow-up assessment, eight sections per brain were evaluated. The authors concluded there was no statistically significant increase in brain tumor incidence. In addition, the FDA commissioned an independent audit of this study by the Universities Associated for Research and Education in Pathology, Inc. (UAREP), a consortium of nine universities recognized for expertise in the area of carcinogenicity testing in animals. The more sophisticated re-evaluation of the brain tumor data did not reveal a statistically significant increase in brain tumors in rats of either sex in this study, and these are the data that regulatory agencies have utilized. Importantly, FDA used a standard and accepted analysis of carcinogenicity studies, including appropriate statistical methods, and determined that there was clearly no dose-dependent increase in brain tumors in this study. Butchko HH, Stargel WW, Comer CP, Mayhew DA, Benninger C, Blackburn GL, de Somerville LMJ, Geha RS, Hertelendy Z, Koestner A, Leon AS, Liepa GU, McMartin KE, Mendenhall CL, Munro IC, Novotny EF, Renwick AG, Schiffman SS, Schomer DL, Shaywitz BA, Spiers PA, Tephly TR, Thomas JA, and Trefz FK (2002) Aspartame: Review of safety. Regul Toxicol Pharmacol 35:S1-93. In 2005, Health Canada stated that the “allegation” that aspartame causes cancer and brain tumors is “not supported.” It elaborated: “Scientists in the world-wide scientific community, including Canadian scientists, have found no link between aspartame consumption and the incidence of cancer or brain tumours from a study of the safety studies performed with aspartame.” (http://www.hc-sc.gc.ca/fn-an/securet/addit/sweeten-edulcor/aspartame-eng.php).
discounted rat carcinogenicity studies (Soffritti et al., 2005; 2007) conducted by the European Ramazzini Foundation (the Ramazzini or ERF studies).7

Substantial evidence reporting no association between aspartame and cancer also has become available since 2004, including the release of the final reports for the three NTP carcinogenicity studies in transgenic mice, and the publication of analytical epidemiological studies that do not show an association between cancer and aspartame consumption (Lim et al. 2006; Gallus et al., 2007). The epidemiological studies and NTP carcinogenicity studies substantially increase the weight of the scientific evidence that aspartame does not present a carcinogenic hazard to humans. Based on this new evidence, the priority for aspartame could be lower today than it was in 2004, when it was assigned a “not high” priority.

Although the authors of the Ramazzini studies reported that aspartame caused cancer in rats in their studies, many others have disagreed with the authors’ conclusions. The Ramazzini studies are seriously flawed, and their results conflict with other carcinogenicity studies of aspartame. Importantly, the Ramazzini studies have been evaluated by several independent regulatory and scientific organizations. These independent reviews have concluded that the Ramazzini studies do not present any credible evidence of carcinogenicity for many reasons. A detailed discussion of the Ramazzini studies appears below in section V.C. of this submission.

IV. Recent reviews by highly-respected regulatory and scientific organizations support the lowest level of carcinogenicity concern.

The potential carcinogenicity of aspartame has been thoroughly reviewed by many well-respected regulatory and scientific organizations. This section summarizes several recent reviews from well-respected scientific bodies that have extensively studied aspartame and are collectively responsible for ensuring the safety of food ingredients for over 825 million consumers.

A. European Food Safety Authority

For many years, the European Food Safety Authority (EFSA) has closely monitored the carcinogenicity studies of aspartame, and it has published a series of reviews of aspartame. The most recent of these EFSA reviews is dated March 19, 2009 and was published on April 20, 2009.8 The EFSA review considered all of the available scientific

evidence on the potential carcinogenicity of aspartame, including both of the Ramazzini rat studies. Notably, this very recent EFSA review concluded:

“Overall, the Panel concluded, on the basis of all the evidence currently available including the last published ERF [Ramazzini] study that there is no indication of any genotoxic or carcinogenic potential of aspartame and that there is no reason to revise the previously established ADI for aspartame of 40 mg/kg bw/day.”

Thus, the recent EFSA review finds no indication of any carcinogenic potential, which supports the CCC’s request to assign aspartame the lowest possible priority for further review.

B. U.S. Food and Drug Administration

The FDA approved aspartame as safe for use in food products as a flavor enhancer and sweetener in 1981. It established an Acceptable Daily Intake (ADI) of 50 mg/kg bw/day for aspartame.

The FDA addressed recent data on carcinogenicity, including the first of the two Ramazzini studies, in an April 2007 reaffirmation of aspartame’s safety:

“FDA reviewed the study data made available to them by ERF and finds that it does not support ERF’s conclusion that aspartame is a carcinogen. Additionally, these data do not provide evidence to alter FDA’s conclusion that the use of aspartame is safe.”

So, the FDA review supports assigning aspartame the lowest possible priority for further review.

C. Aspartame Expert Panel Report

An independent panel of recognized experts (the Expert Panel) assessed the safety status of aspartame, including all of the available animal and epidemiological studies of aspartame relating to cancer. The Expert Panel was chaired by Dr. William J. Waddell, University of Louisville Medical School. Other members of the Expert Panel included (in alphabetical order): G.A. Burdock (Burdock Group), J. Doull (U. of Kansas Medical School), R.M. Kroes (Institute for Risk Assessment Sciences, The Netherlands), B.A. Magnuson (Burdock Group), G.M. Marsh (University of Pittsburgh), M.W. Pariza (University of Wisconsin), P.S. Spencer (Oregon Health and Science University), R. Walker (University of Surrey, Great Britain), and G.M. Williams (New York Medical

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9 Id., p. 15 (emphasis added).
College). The toxicology and safety-in-use associated with aspartame were critically evaluated, and this review was published in *Critical Reviews in Toxicology* in 2007.\(^{11}\)

The Expert Panel concluded that the epidemiological studies of aspartame did not demonstrate a link between cancer and aspartame consumption:

“Epidemiological studies on aspartame include several case-control studies and one well-conducted prospective epidemiological study with a large cohort, in which the consumption of aspartame was measured. The studies provide **no evidence to support an association between aspartame and cancer in any tissue**.”\(^{12}\)

With respect to the animal carcinogenicity studies of aspartame, the Expert Panel concluded:

“Critical review of all carcinogenicity studies conducted on aspartame found **no credible evidence that aspartame is carcinogenic**.”\(^{13}\)

“Aspartame is well documented to be **nongenotoxic and there is no credible evidence that aspartame is carcinogenic**.”\(^{14}\)

This conclusion was based on all of the animal carcinogenicity studies of aspartame, except for the second Ramazzini study, which was published in 2007. Subsequently, the Expert Panel also reviewed the second Ramazzini study in an addendum to its report, which was also included in the peer-reviewed publication.\(^{15}\) In the Addendum, the Expert Panel concluded:

“In summary, considering the lack of significant differences between high dose groups and historical control cancer rates, plus the many deficits in the study design and data, it is the opinion of this expert panel that this study (Soffritti et al., 2007) **fails to provide convincing evidence of aspartame carcinogenicity**.”\(^{16}\)

**D. United Kingdom**

As with other independent experts, the United Kingdom Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment reviewed the first Ramazzini study and did not consider it credible evidence of carcinogenicity: “In view of


\(^{12}\) Id. P. 630 (emphasis added).

\(^{13}\) Id., p. 630 (emphasis added).

\(^{14}\) Id., p. 702 (emphasis added).

\(^{15}\) Id., p. 702-3.

\(^{16}\) Id., p. 703 (emphasis added).
the inadequacies in design of the ERF study and the use of rats with a high concurrent infection rate, the COC considered that no valid conclusions could be derived from it.\textsuperscript{17}

In summary, the critical reviews by EFSA, FDA, the Expert Panel, the UK Committee on Carcinogenicity of Chemicals in Food, and Health Canada\textsuperscript{18} provide overwhelming support for assigning the lowest priority status to aspartame. These independent reviews have consistently emphasized that \textit{no} credible evidence of carcinogenicity exists.

\section*{V. There is no credible evidence that aspartame causes cancer in animals.}

There are at least nine carcinogenicity studies of aspartame reported to date. None of these studies presents credible evidence that aspartame causes cancer in animals. The results of the animal carcinogenicity studies of aspartame are summarized in Table 1.

\subsection*{A. Carcinogenicity Studies in Rats and Mice (1973-1981)}

No carcinogenic effects were reported in a total of four 2-year carcinogenicity studies in rats and mice reported between 1973-1981. Only one of these studies (i.e., the two-year Hazelton study in CD rats) was mentioned by OEHHA in the Background Document. However, there were three additional carcinogenicity studies in rats and mice reported between 1973 and 1982, including:

1. a second Hazelton 2-year carcinogenicity study in CD rats that included \textit{in utero} and postnatal exposure,\textsuperscript{19}

2. a large carcinogenicity study in SLC Wistar rats conducted in Japan that used 86 rats/sex/dose,\textsuperscript{20} and

3. a 2-year Hazelton carcinogenicity study in CD-1 mice.\textsuperscript{21}

None of these four carcinogenicity studies in rats and mice found an increase in tumors attributable to aspartame. All of these studies were conducted for the purpose of supporting regulatory approval of aspartame. In the U.S., carcinogenicity studies of aspartame were submitted to and reviewed by the FDA. In addition, at FDA’s request, these studies were audited by the Universities Associated for Research and Education in Pathology, Inc.

In summary, these four studies provide no evidence of carcinogenicity.

\textsuperscript{18} See footnote 6, above.
\textsuperscript{19} Trutter and Reno (1973)
\textsuperscript{20} Ishi et al., (1981)
\textsuperscript{21} Searle Laboratories, E75 (1974)
B. **NTP (2005) Carcinogenicity Studies in Transgenic Mice**

The National Toxicology Program, a body identified by the CIC as authoritative on Proposition 65 cancer issues,\(^{22}\) recently conducted three carcinogenicity studies of aspartame using three different transgenic mouse models.\(^{23}\) None of the NTP carcinogenicity studies is mentioned in the Background Document. The conclusion of each study was that “there was no evidence of carcinogenicity of aspartame.”

The protocol was identical for each of the NTP studies. The three models used were the heterozygous p53-deficient (+/−) mouse (sensitive for spontaneous lymphomas and sarcomas), the Cdkn2a-deficient mouse (claimed to be sensitive for suspected brain carcinogens), and the Tg.AC mouse (detection of both genotoxic and nongenotoxic carcinogens and in particular sensitive for forestomach tumors). The NTP said it studied aspartame in these three transgenic or genetically manipulated mouse strains, “because this model is proposed to be susceptible to glial cell tumors of the brain.”\(^{24}\) The six concentration levels used were 0, 3125, 6250, 12,500, 25,000, and 50,000 ppm aspartame in NTP 2000 feed.

In all three studies, there were no tumors attributed to exposure to aspartame in either sex at any dose tested. In short, no evidence of carcinogenicity was observed in these NTP transgenic mouse model studies with dietary levels of aspartame equivalent to 7500 mg/kg bw/day.

C. **Ramazzini Carcinogenicity Studies in Rats (Soffritti et al., 2005; 2007)**

The authors of the two Ramazzini rat carcinogenicity studies suggested that aspartame had the potential to produce combined leukemia/lymphoma in rats. These studies, however, have multiple, serious problems with experimental design, interpretation of results and data reporting. Independent reviews have been highly critical of these two studies for many valid reasons. No regulatory agency has considered the Ramazzini aspartame studies to be credible evidence of carcinogenicity, and no regulatory agency has ever relied upon the Ramazzini studies of aspartame for regulatory purposes.


EFSA conducted a comprehensive review of aspartame in January 2009 that included a detailed review of the second Ramazzini study (Soffritti et al., 2007). The EFSA Panel requested information from the authors of the Ramazzini studies to assist in its evaluation. Initially, the Ramazzini authors chose not to fulfill EFSA’s data request. Subsequently, the Ramazzini authors provided only a portion of the detailed data requested by EFSA. After carefully reviewing the Ramazzini studies, EFSA stated:

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\(^{22}\) 27 CCR § 25306(m)(3).


“Overall, the Panel concluded, on the basis of all the evidence currently available from the results published from the ERF [Ramazzini] studies and previous [EFSA] evaluations, that there is no indication of any genotoxic or carcinogenic potential of aspartame and that there is no reason to revise the previously established ADI for aspartame of 40 mg/kg bw/day.”

EFSA explained its evaluation of the Ramazzini studies in great detail. With respect to the increased incidence of lymphoma and leukemia, one of the key criticisms of the two Ramazzini studies is that the rats were housed under crowded conditions and had an unusually high incidence of a chronic lung disease, which presents lesions that can be misdiagnosed as lymphoma. EFSA stated:

“Evaluation of aggregated malignant tumour incidences as evidence of carcinogenic potential of the test compound can only be performed based on a thorough consideration of all tumour data including onset, and data on non-neoplastic, hyperplastic and preneoplastic lesions but these data were not provided by the authors. Limited information on the presence of inflammatory changes in the lungs of animals with lymphomas and leukemias were provided by the ERF in the additional submission [by the authors of the Ramazzini studies in February 2009].

“The majority of the lymphomas and leukemias observed appeared to have developed in rats suffering from inflammatory changes in the lungs which is characteristic for chronic respiratory disease. In accordance with the previous view of the AFC Panel, the Panel concluded that these changes were not related to the treatment with aspartame.”

In May 2006, after the first Ramazzini study was published, EFSA thoroughly critiqued the first study:

“After its evaluation the Panel considers that the study has flaws which bring into question the validity of the findings, as interpreted by the ERF. In particular, the high background incidence of chronic inflammatory changes in the lungs and other vital organs and tissues and the uncertainty about the correctness of the diagnoses of some tumour types were major confounding factors in the interpretation of the findings of the study.”


27 European Food Safety Authority, Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (FAC) on a request from the Commission related to a

Schoeb, et al., (2009) recently published a letter to the editor of the journal *Environmental and Molecular Mutagenesis* specifically addressing the diagnosis of tumors in the Ramazzini studies of aspartame and another chemical. The authors of the Letter to the Editor were: T.R. Schoeb (U. of Alabama at Birmingham), E.E. McConnell (ToxPath, Inc.), M.M. Juliana (U. of Alabama at Birmingham), J.K. Davis (Purdue U.), M.K. Davidson (FDA), and J.R. Lindsey (Emeritus, U. of Alabama at Birmingham). The authors concluded that the Ramazzini studies misclassified lesions as lymphoma that were actually lesions due to pulmonary disease.

“Moreover, the cellular morphology shown in ERF publications for these neoplasms [Belpoggi et al., 1999; Soffritti et al., 2005] is more pleomorphic than is typical of lymphoma in rats, and the lesions appear to contain neutrophils. We believe that lesions characterized by accumulation of lymphocytes, plasma cells, and neutrophils in the lungs of conventional rats are much more likely to be due to M. [Mycoplasma] pulmonis disease than to chemical induction of a rare type of lymphoma with an uncharacteristic organ distribution. Consequently, we furthermore believe that the reported induction of lymphoma by aspartame and MTBE probably is the result of exacerbation of M. [Mycoplasma] pulmonis disease by chemical treatment and misdiagnosis of the lesions as lymphoma.”

This evaluation disputes the allegation of the Ramazzini study authors that aspartame causes cancer. Schoeb, et al. have submitted a full article on this topic to the same journal.


Both Ramazzini studies were reviewed in detail by the Expert Panel. When the Expert Panel report was first written, the second Ramazzini study had not yet been published. When the second Ramazzini study was released, the Expert Panel analyzed this study in an Addendum to their report. In both cases, the Expert Panel identified numerous shortcomings in the study design and conduct. The Expert Panel summarized its evaluation of the second Ramazzini study as follows:

“considering the lack of significant differences between high dose groups and historical control cancer rates, plus the many deficits in the study design and data, it is the opinion of this expert panel that this study

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(Soffritti et al., 2007) fails to provide convincing evidence of aspartame carcinogenicity.”

Regarding the first Ramazzini study (i.e., Soffritti et al., 2005), the Expert Panel stated:

“In summary, the Soffritti [Ramazzini] reports alleging carcinogenicity are contradicted by many publications and every scientific consideration. Many potential flaws have been suggested in this report; whether these or some other unidentified flaw is responsible for their incorrect allegations is not known. Nevertheless, it can be confidently stated that these reports provide no credible evidence that aspartame is carcinogenic.”

The Expert Panel identified multiple flaws in the first study. A partial list of the defects identified by the Expert Panel includes:

- Very high incidence of infection in rats (e.g., bronchopneumonia in 81-95% of males and 69-97% of females)
- Rats were housed five per cage (high-density housing may have contributed to the high incidence of infections)
- Different groups were housed in different animal rooms (possibly accounting for differences in survival and results)
- Low survival rates at 104 weeks, which are likely due to the very high incidence of infection
- Duration of study was unconventional (rats were allowed to live until spontaneous death)
- NTP pathology review of slides confirmed the presence of autolytic tissue changes in the animals found dead
- Tumors from different tissues were inappropriately combined for analysis
- Causes of death not reported
- Most of the histopathological results were not included in the report
- No randomization of rats assigned to groups
- No information on the composition of the diet
- No adjustment of diet for the decrease in vitamins and mineral content due to the addition of aspartame
- Multiple problems with the statistical analyses of the data

Based on the review of the Ramazzini studies by the Expert Panel, it is evident that the Ramazzini studies do not represent “scientifically valid testing.” While the issue at hand is prioritization, it is interesting to note that, in order to list a chemical, it must be clearly shown through “scientifically valid testing” to cause cancer.

30 Id. at p. 669 (emphasis added).
4. **FDA Review of the Ramazzini Studies**

As noted above in Section IV.B, FDA did not consider the first Ramazzini study credible evidence of carcinogenicity, and has published the findings of their review. Excerpts from their review included:

“FDA requested the data from ERF to evaluate the findings. On February 28, 2006, the agency received only a portion of the study data requested. In June 2006, FDA asked ERF to provide the remainder of the study data initially requested and also offered to review pathology slides from the study. ERF did not submit additional data to FDA and did not agree to FDA’s review of the pathology slides.

“... Based on the available data ... we have identified significant shortcomings in the design, conduct, reporting, and interpretation of this study. FDA finds that the reliability and interpretation of the study outcome is compromised by these shortcomings and uncontrolled variables, such as the presence of infection in the test animals.

... Considering results from the large number of studies on aspartame’s safety, including five previously conducted negative chronic carcinogenicity studies, a recently reported large epidemiology study with negative associations between the use of aspartame and the occurrence of tumors, and negative findings from a series of three transgenic mouse assays, FDA finds no reason to alter its previous conclusion that aspartame is safe as a general purpose sweetener in food.”

**VI. Genotoxicity data further lowers the carcinogenicity concern.**

The overwhelming weight of the scientific evidence indicates that aspartame is not genotoxic. The genotoxic potential of aspartame has been extensively evaluated in microbial, cell culture, and whole animal models. A summary of the genotoxicity studies of aspartame appears in Table 24 of the Expert Panel report. The Expert Panel concluded:

“Extensive in vitro and in vivo studies provide ample evidence that aspartame is nongenotoxic.”

“Aspartame is well documented to be nongenotoxic and there is no credible evidence that aspartame is carcinogenic.”

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33 Magnuson et al., 2007, p. 687.  
34 Id., p. 688 (emphasis added).  
35 Id., p. 702 (emphasis added).
As noted earlier, the 2009 EFSA review concluded:

“Overall, the Panel concluded, on the basis of all the evidence currently available including the last published ERF [Ramazzini] study that there is no indication of any genotoxic or carcinogenic potential of aspartame…”  

The weight of the scientific evidence, including many in vitro and in vivo studies in animals, indicates that aspartame is not genotoxic.

VII. There is no credible evidence that aspartame causes cancer in humans.

There is no evidence of carcinogenicity in humans with the exception of a single ecological study that reported an increase in brain tumors that coincided with the introduction of aspartame in foods. This study, representing a classic example of the “ecological fallacy,” was questioned and criticized by many scientists for a wide variety of reasons. Subsequently, many well-conducted epidemiological (analytical) studies of aspartame have been conducted, and these studies reveal no link between cancer and aspartame consumption.

A large (n = 473,984), prospective cohort study from the U.S. National Cancer Institute found no cancer incidence linked to aspartame consumption. The study evaluated approximately 500,000 men and women and found (compared to those who did not consume aspartame) that there was no evidence of an increased risk of leukemias, lymphomas, and brain tumors among those who used aspartame.

An additional study published by Italian and French researchers found no association between aspartame and cancer in humans. The researchers evaluated a variety of studies, published between 1991 and 2004 in over 7000 men and women. The researchers noted “In conclusion, therefore, this study provides no evidence that saccharin or other sweeteners (mainly aspartame) increase the risk of cancer at several common sites in humans.”

The Expert Panel review did not reveal any link between cancer and aspartame consumption:

“In conclusion, case-control studies and one well-conducted prospective epidemiological study with a large cohort, in which the consumption of

37 Olney et al., 1996.
38 Lim, 2006.
39 Gallus et al., 2007.
aspartame was measured, provided no evidence to support an association between aspartame and brain or hematopoietic tumor development.\footnote{40}

VIII. Conclusion

For the reasons stated above, the Calorie Control Council respectfully requests that aspartame be identified as having the lowest possible priority for further carcinogenicity review.

\footnote{40 Magnuson et al. (2007), p. 699.}
<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
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<td>Searle, E33/34 (Trutter and Reno, 1973)</td>
<td>Sprague-Dawley CD Rat</td>
<td>0, 1, 2, 4, 6-8</td>
<td>2 yr</td>
<td>Not carcinogenic</td>
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</tr>
<tr>
<td>Searle, E70 (Trutter and Reno, 1973)</td>
<td>Sprague-Dawley CD Rat</td>
<td>0, 2, 4</td>
<td>In utero, lactation and 2 yr</td>
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<tr>
<td>Searle, E87 (McConnell, 1973)</td>
<td>CD-1 Mouse</td>
<td>0, 1, 2, 4</td>
<td>2 yr</td>
<td>Not carcinogenic</td>
<td></td>
</tr>
<tr>
<td>Ishii et al. (1981)</td>
<td>SLC Wistar Rat</td>
<td>0, 1, 2, 4</td>
<td>2 yr</td>
<td>Not carcinogenic</td>
<td></td>
</tr>
<tr>
<td>NTP (2005)</td>
<td>Heterozygous p53-deficient Mouse</td>
<td>0, 0.5, 1, 2, 4, 8</td>
<td>9 mo</td>
<td>Not carcinogenic</td>
<td>Sensitive for spontaneous lymphomas and sarcomas</td>
</tr>
<tr>
<td>NTP (2005)</td>
<td>Cdkn2a-deficient Mouse</td>
<td>0, 0.5, 1, 2, 4, 8</td>
<td>9 mo</td>
<td>Not carcinogenic</td>
<td>Sensitive for brain tumors</td>
</tr>
<tr>
<td>NTP (2005)</td>
<td>Tg.AC Mouse</td>
<td>0, 0.5, 1, 2, 4, 8</td>
<td>9 mo</td>
<td>Not carcinogenic</td>
<td>Sensitive for genotoxic/nongenotoxic carcinogens</td>
</tr>
<tr>
<td>Soffritti et al. (2005, 2006)</td>
<td>Sprague-Dawley Rat (institutional colony)</td>
<td>0, 0.004, 0.02, 0.1, 0.5, 2.5, 5</td>
<td>Until spontaneous death (varied among groups)</td>
<td>Inc in combined lymphoma/leukemia in females, renal carcinomas, malignant schwannomas of peripheral nerves</td>
<td>Seriously flawed. High incidence of infection. FDA, EFSA and other groups disagreed with conclusions. “No credible evidence” of carcinogenicity.</td>
</tr>
<tr>
<td>Soffritti et al. (2007)</td>
<td>Sprague-Dawley Rat (institutional colony)</td>
<td>0, 0.06, 0.3</td>
<td>In utero, lactation, until spontaneous death (varied among groups)</td>
<td>Inc in (a) malignant tumors in males, (b) lymphoma/leukemia in males &amp; females, (c) mammary cancer in females</td>
<td>Seriously flawed. High incidence of infection. Heavily criticized by EFSA and other groups. “No credible evidence” of carcinogenicity.</td>
</tr>
</tbody>
</table>
On October 17, 2003, OEHHA announced the release of draft priority assignments and draft data summaries for 47 of 50 chemicals (“Batch 4”) selected for prioritization with respect to their potential to cause cancer. Final priority assignments and data summaries for 45 of the 47 chemicals for which draft priorities had been assigned are presented here. Final data summaries for the two remaining chemicals (nucleoside analogues, titanium dioxide) are still under preparation. Draft data summaries and priorities were not released last October on three postponed substances: chromium picolinate, toxins derived from Fusarium moniliforme (Fusarium verticillioides), and sodium nitrite. Chromium picolinate was postponed pending the results of a bioassay expected from the National Toxicology Program. “Toxins derived from Fusarium moniliforme” was postponed because it is a candidate for listing via the authoritative bodies mechanism. The draft data summary and priority status for sodium nitrite is under development.

As in previous prioritizations, the 50 Batch #4 chemicals were randomly selected from 100 chemicals in the tracking database. The 100 chemicals consisted of the 39 chemicals remaining from the previous random selection and 61 additional chemicals selected using a table of random numbers from among those chemicals in the database that are produced, used, released or present in California, and for which there is some information suggesting the chemicals may be carcinogenic.

Prioritization of chemicals proceeded as described in the document entitled “Procedure for Prioritizing Candidate Chemicals for Consideration Under Proposition 65 by the State's Qualified Experts” (May 1997). The October 17, 2003 release initiated a 60-day public comment period, which included a public workshop held November 19, 2003. After review and careful consideration of the comments received, the priority assignments have been finalized for 45 of the 47 chemicals.

Prioritized chemicals with a final priority of “High” Carcinogenicity Concern are assigned to the Candidate List, from which chemicals will be chosen for the preparation of hazard identification documents. All chemicals not assigned a final “high” level of carcinogenic concern are assigned to Category II. Action is not anticipated on Category II chemicals until all high priority chemicals on the Candidate List with known or potential exposure have been evaluated.

It should be noted that (1) this prioritization process reflects a preliminary, rather than an in-depth review of carcinogenicity and exposure data, and, (2) the process is a continuous one; efforts to gather additional information on Category I and Category II chemicals are ongoing.
<table>
<thead>
<tr>
<th>Name of Chemical</th>
<th>CAS No.</th>
<th>Level of Exposure Concern</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On Candidate List due to HIGH CARCINOGENICITY CONCERN</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4-Amino-N-(4,6-dimethyl-2-pyrimidinyl)benzene sulfonamide (sulfamethazine)</td>
<td>57-68-1</td>
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<tr>
<td>3,6-Dinitrobenzo[a]pyrene</td>
<td>128714-76-1</td>
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<tr>
<td>1,2-Epoxybutane</td>
<td>106-88-7</td>
<td>high</td>
<td>7</td>
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<tr>
<td>Methimazole</td>
<td>60-56-0</td>
<td>high</td>
<td>9</td>
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<tr>
<td>Molybdenum trioxide</td>
<td>1313-27-5</td>
<td>high</td>
<td>11</td>
</tr>
<tr>
<td>4-Nitrotoluene (p-nitrotoluene)</td>
<td>99-99-0</td>
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<td>13</td>
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<tr>
<td>Propoxur (Baygon)</td>
<td>114-26-1</td>
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<td>15</td>
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<tr>
<td>1,2,4-Trichlorobenzene</td>
<td>120-82-1</td>
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<tr>
<td>Verapamil</td>
<td>52-53-9</td>
<td>high</td>
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<tr>
<td>2-Chloro-1,1,1-trifluoroethane</td>
<td>75-88-7</td>
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<td>4-Hydroxybenzenediazonium and its salts</td>
<td>19089-85-1</td>
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<tr>
<td>4-Methylbenzenediazonium and its salts</td>
<td>57573-52-1</td>
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<tr>
<td>Ciprofibrate</td>
<td>52214-84-3</td>
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<td>Diallylate</td>
<td>2303-16-4</td>
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<td>Diftalone</td>
<td>21626-89-1</td>
<td>n.i.c.</td>
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<td><strong>Category II (Not HIGH CARCINOGENICITY CONCERN)</strong></td>
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<tr>
<td>Acephate</td>
<td>30560-19-1</td>
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<tr>
<td><em>trans</em>-Anethole</td>
<td>4180-23-8</td>
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<td>33</td>
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<tr>
<td>Aspartame</td>
<td>22839-47-0</td>
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<td>35</td>
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<tr>
<td>Chloroacetic acid</td>
<td>79-11-8</td>
<td>high</td>
<td>38</td>
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<tr>
<td>Chloromethane (methyl chloride)</td>
<td>74-87-3</td>
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<tr>
<td>Cholestryramine</td>
<td>11041-12-6</td>
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<tr>
<td>Clofentezine</td>
<td>74115-24-5</td>
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<td>Cycloate</td>
<td>1134-23-2</td>
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<tr>
<td>3,4-Dihydrocoumarin</td>
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<tr>
<td>Flutamide</td>
<td>13311-84-7</td>
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<tr>
<td>Isoniazid</td>
<td>54-85-3</td>
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<td>50</td>
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<tr>
<td>Levobunololol and its salts</td>
<td>47141-42-4</td>
<td>high</td>
<td>52</td>
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<tr>
<td>Methyl methacrylate</td>
<td>80-62-6</td>
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<td>53</td>
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<tr>
<td>Mineral fibers, man-made; now referred to as Synthetic vitreous fibers:</td>
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<tr>
<td>Rockwool (stonewool)</td>
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<td>high</td>
<td>55</td>
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<tr>
<td>Slagwool</td>
<td>-----</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Continuous glass filaments</td>
<td>-----</td>
<td>high</td>
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<tr>
<td>Nicotine</td>
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</tr>
<tr>
<td>Name of Chemical</td>
<td>CAS No.</td>
<td>Level of Exposure</td>
<td>Page</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>-----------</td>
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<tr>
<td>3-Nitrofluoranthene</td>
<td>892-21-7</td>
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<tr>
<td>Orlistat</td>
<td>96829-58-2</td>
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<tr>
<td>Oxyfluorfen (Goal)</td>
<td>42874-03-3</td>
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<tr>
<td>Pyrimethamine (Daraprim)</td>
<td>58-14-0</td>
<td>high</td>
<td>65</td>
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<td>Triethanolamine</td>
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<tr>
<td>Vitamin K (by intramuscular injection in neonates)</td>
<td>12001-79-5</td>
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<td>69</td>
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<tr>
<td>Dimethipin (Harvade)</td>
<td>55290-64-7</td>
<td>medium</td>
<td>71</td>
</tr>
<tr>
<td>Mecoprop and its salts</td>
<td>7085-19-0</td>
<td>medium</td>
<td>73</td>
</tr>
<tr>
<td>Tralkoxydim</td>
<td>87820-88-0</td>
<td>medium</td>
<td>75</td>
</tr>
<tr>
<td>Triflusulfuron-methyl</td>
<td>126535-15-7</td>
<td>medium</td>
<td>76</td>
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<tr>
<td>Indolidan</td>
<td>100643-96-7</td>
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<tr>
<td>Isomazole and isomazole hydrochloride</td>
<td>86315-52-8; 87359-33-9</td>
<td>low</td>
<td>79</td>
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<tr>
<td>Acetoxymethylphenylnitrosamine</td>
<td>81943-37-5</td>
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<td>1-Benzoyl-2,6-dimethyl-4-nitrosopiperazine</td>
<td>61034-40-0</td>
<td>n.i.c.</td>
<td>81</td>
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</tbody>
</table>

**INADEQUATE DATA to establish level of concern**

<table>
<thead>
<tr>
<th>Name of Chemical</th>
<th>CAS No.</th>
<th>Level of Exposure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimozide</td>
<td>2062-78-4</td>
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</table>

**POSTPONED**

<table>
<thead>
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<th>Name of Chemical</th>
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<tr>
<td>Chromium picolinate</td>
<td>14639-25-9</td>
<td>Awaiting completion of NTP bioassays</td>
</tr>
<tr>
<td><em>Fusarium moniliforme (Fusarium verticillioides), toxins derived from</em></td>
<td>-----</td>
<td>Candidate for administrative listing</td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>7632-00-0</td>
<td>Review being completed</td>
</tr>
</tbody>
</table>

n.i.c. = No Identified Concern
CARCINOGENICITY DATA SUMMARY: ASPARTAME

Preliminary evaluation of carcinogenicity and exposure data

Aspartame [Equal®; NutraSweet®; L-aspartyl-L-phenylalanine methyl ester; CAS No. 22839-47-0] did not reach a level of carcinogenicity concern sufficient to be placed on the candidate list. There is, however, some carcinogenicity concern over observations of brain tumors in aspartame-treated rats. Reliable animal studies have not been conducted despite the widespread human exposure to this artificial sweetener. Epidemiologic data provide inadequate information on which to judge carcinogenicity. One small epidemiologic study found no evidence of an effect of aspartame consumption on brain tumor risk in children. Aspartame has been suggested as an explanation for increased rates of human brain cancer. Further epidemiologic and toxicologic studies are needed on the carcinogenicity of this chemical.

No large epidemiological studies of carcinogenicity have been conducted. Olney et al. (1996), performing a descriptive analysis of national cancer data, suggested the possibility that aspartame might be associated with increased incidence of brain tumors in the U.S. A small study (Gurney et al., 1997) of aspartame consumption in children and brain tumor risk found no evidence that cases (n=56) were more likely to consume foods containing aspartame than controls (n=90).

There have been multiple carcinogenicity studies of aspartame in animals, each of which is inadequate for judging carcinogenicity. Searle Laboratories has conducted two sets of studies in rats. In the first set, referred to as Study E-33/34, female and male Charles River CD Sprague-Dawley albino rats were fed 0, 1, 2, 4, or 8 g/kg aspartame daily for 104 weeks. In female rats, one 4 g/kg dose animal was observed with brain tumor (ependymoma) and three high dose females were (2 meningioma, 1 glioma) (Searle Laboratories, 1973). The brain tumor incidences in the Searle Laboratories (1973) report (number of tumors/number of animals examined) in the 0, 1, 2, 4, and 8 g/kg females were 0/59, 0/4, 0/4, 1/4, 3/39, respectively, a statistically significant increase with increasing dose (p = 0.0206, Fisher Exact trend test; p = 0.0167, Cochran-Armitage trend test). In male rats, one brain tumor, a meningioma, was observed in the high dose group. The incidences were: 0/58, 0/4, 0/3, 0/1, 1/40 (Searle Laboratories, 1973). Searle Laboratories (1973) reported that these findings were not statistically significant (although Fisher Exact trend test for females indicates otherwise). The FDA Commissioner (1981) noted “variations in tumor count among the several persons or groups who viewed the slides.” The FDA’s Public Board of Inquiry (PBOI) reported the following brain tumors incidences (number of tumors/“total number of animals at risk”): females, 0/59, 2/40, 0/40, 1/40, 2/38; males, 1/59, 2/40, 0/40, 1/40, 2/38. These data, as reported by the PBOI, do not reflect the limited numbers of animals examined for brain histopathology in the low-, mid-, and mid-high-dose groups of both sexes, nor do these data reflect a significant increase in brain tumors with increasing dose in females. The PBOI expressed concern over the early occurrence of brain tumors in some animals (FDA Commissioner, 1981). There was disagreement among examining pathologists as to the positive finding in the male control group, with one of three finding no tumor (FDA Commissioner, 1981). The PBOI also considered historical background incidence of brain tumors in interpreting the study findings, and concluded that the available data did not rule out the possibility that aspartame might induce brain tumors (FDA Commissioner, 1981).

In the second set of Searle Laboratory studies, referred to as study E-70, aspartame was fed to female Charles River Sprague-Dawley rat dams during pregnancy and lactation and to their offspring after weaning for 104 weeks. Daily dose levels were 0, 2, and 4 g/kg. Five of 160 aspartame-fed rats and four of 120 controls were reported with brain tumors. Hyperplastic liver nodules were increased in treated females. An FDA review panel concluded that Searle Laboratories did not employ a feed analysis program to monitor their incorporation of test compound into feed. FDA’s PBOI (Nauta et al., 1980) considered this a deficient study (FDA Commissioner, 1981).

Ishii (1981) fed groups of SCL Wistar rats 0, 1, 2 or 4 g/kg aspartame, or 4 gm/kg aspartame + diketopiperazine (DKP) (3:1) for 104 weeks and evaluated brain tumorigenicity. Interim sacrifice included 10 animals/sex/group at 26 weeks and 16 animals/sex/group at 52 weeks. No brain tumors were observed in the interim sacrifice animals. Total number of animals in the main groups was 60 sex/group; the number surviving to 104 weeks was reduced in some groups to as few as 16 (1 g/kg males), and in all groups was less than 30 in males and lower in males than females. Among females, one control had an “atypical astrocytoma”; two brain tumors were found at 2 g/kg (1 astrocytoma, 1 ependymoma) and one at 4 g/kg (oligodendroglioma). In males, one treated at 1 mg/kg was found with oligodendroglioma and one at 4 g/kg with astrocytoma.

Studies in mice fed aspartame in diet found no indication of increased tumor incidence (FDA Commissioner, 1981). Details of study results have not been published.
The National Toxicology Program (NTP, 2003a) has conducted non-standard bioassays in both sexes of genetically altered (p53 haploinsufficient) mice. Animals in groups of 15 were fed aspartame for nine months at feed concentrations ranging from 3,125 to 50,000 ppm. There was no evidence of treated-related carcinogenicity. This provides limited information on the potential for aspartame to induce cancer in humans; group sizes were small and the use of the genetically altered mouse is a new model. Thus, there is uncertainty as to whether the study possessed sufficient sensitivity to detect a carcinogenic effect (NTP, 2003b).

Aspartame breaks down spontaneously to diketopiperazine (DKP), which normally comprises less than 2% of the final aspartame product (FDA Commissioner, 1981). DKP was tested for brain tumorigenic activity in Sprague-Dawley rats fed DKP for 115 weeks (FDA Commissioner, 1981), in a study referred to as E-77/78, at doses of 0, 0.75, 1.5, and 3.0 g/kg. No increased incidence of brain tumors compared to untreated rats was observed. An FDA inspection team investigated the laboratory carrying out this study and found irregularities that included evidence of improper feed mixing (the chow was ground to a fine powder, but the DKP was present in large chunks), which may have allowed the rats to avoid eating the DKP (Bressler, 1977). The team also noted methodological quality control issues that could impact on the study findings.

The promoting potential of aspartame on urinary bladder carcinogenesis, initiated with N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN), was studied in male F344 rats who received 0.01% BBN in drinking water for four weeks followed by 5% aspartame in the diet for 32 weeks (total aspartame intake, 400 gm/kg). The incidences of bladder lesions were not increased in the 28 rats surviving to the end of the experiment, 36 weeks (Hagiwara et al., 1984).

Aspartame was not mutagenic in TA 100 and TA 98 Salmonella tester strains (Shephard et al., 1993). Aspartame, nitrosated in vitro (to simulate the nitrosation that occurs in the stomach), was mutagenic towards TA100, TA104, and TA98 without metabolic activation, but not toward TA102 (Shephard et al., 1993). Aspartame was not clastogenic, in vivo, in mice (Durnev et al., 1995). Jeffrey and Williams (2000) reported that aspartame in vitro did not induce DNA synthesis in rat hepatocytes. Mukhopadhyay et al. (2000) report in vivo co-exposure of aspartame and acesulfame potassium was negative for the induction of chromosome aberrations in male Swiss mice bone marrow cells. Aspartame adducts were found in nucleic acids and proteins from aspartame-fed rats, and the authors concluded aspartame-derived formaldehyde was responsible for adduct formation (Trocho et al., 1998).

There is a HIGH level of concern over the extent of exposure to aspartame. Aspartame is a low-calorie sweetener, first approved in 1981, currently consumed by more than 100 million people around the world (Calorie Control Council, 2002). In the U.S., aspartame is available for use in more than 1500 products, including table-top sweeteners, carbonated beverages, baked goods, chewable multi-vitamins, hot and cold breakfast cereals, chewing gum, puddings and fillings, candies, cough drops, pharmaceuticals, and many other products (Calorie Control Council, 2002). The “acceptable daily intake” of aspartame, established by FDA, is 50 mg/kg; a food intake survey conducted by U.S. Department of Agriculture found some people in the U.S. consumed more than 16 mg/kg/day (Butchko et al., 1994).

References


