Appendix E-2.41: Evidence Portfolio

Part D. Chapter 5: Food Sustainability and Safety

What is the relationship between aspartame consumption and health?

Conclusion Statement: The DGAC generally concurs with the European Food Safety Authority (EFSA) Panel on Food Additives that aspartame in amounts commonly consumed is safe and poses minimal health risk for healthy individuals without phenylketonuria (PKU).
DGAC Grade: Moderate

Limited and inconsistent evidence suggests a possible association between aspartame and risk of some hematopoietic cancers (non-Hodgkin lymphoma and multiple myeloma) in men, indicating the need for more long-term human studies. In addition, limited and inconsistent evidence indicates a potential for risk of preterm delivery. Due to very limited evidence it is not possible to draw any conclusions on the relationship between aspartame consumption and headaches.
DGAC Grade: Limited

Key Findings

- Overall, intakes of aspartame are not associated with an increased risk of adverse outcomes in populations who do not have PKU.
- Some concern requiring further investigation exist for some cancers, especially hematopeitic ones, but the data do not clearly identify a relationship.
- The possibility that intakes amongst the higher exposure groups during pregnancy could be associated with preterm delivery requires further evaluation and research.
- Overall exposures up to 40 mg/kg/day do not pose safety concerns based on modeling of evidence-based safe blood levels in a dose-response model.
- Intakes exceeding this amount are uncommon in the US population (need to quantify if possible).
- It must be emphasized that these findings do not apply to individuals with the disease PKU.

Description of the Evidence

European Food Safety Authority (EFSA) Report on the Scientific Opinion on the Re-evaluation of Aspartame as a Food Additive; EFSA Panel of Food Additives and Nutrient Sources added to Food (ANS), January 2013

Background

Aspartame is the most common low-calorie sweeteners used in the United States. It is found in numerous dietary sources. Although most commonly associated with low-calorie/low-sugar versions of carbonated and non-carbonated beverages, it also is found in low-calorie/low-sugar versions of canned fruits and juices; instant cereals; baked goods; ice cream and frozen ices; candy and chocolate products; jams, jellies, syrups, and condiments; yogurt; and beer. Nonnutritive sweeteners are regulated by the FDA. The FDA has concluded that aspartame is safe as a general purpose sweetener in food. Given the high interest of the public in the safety of aspartame, the DGAC reviewed the EFSA report on the sweetener and health outcomes.

Evidence Synthesis

The most recent European Food Safety Authority (EFSA) report on the re-evaluation of aspartame as a food additive was used to address this question. The EFSA report based its evaluation on original study reports and information submitted following public calls for data, previous evaluations, and additional literature that became available up until the end of public consultation on Nov 15, 2013. The DGAC focused on results from human studies, not animal studies or studies conducted *in vitro*. The Mode of Action (MoA) analysis on reproductive and developmental toxicity of aspartame was also included. Although the EFSA report considered both published and unpublished studies, the DGAC only considered published studies.

Cancer

A relatively limited body of evidence on human studies has directly addressed the relationship between aspartame consumption and cancer risk. The most consistent finding in six U.S. and European case-control studies (Andreatta 2008; Bosetti 2009; Bunin 2005; Cabaniols 2011; Gallus 2006; Hardell 2001) was the absence of an adverse relationship between consumption of low-calorie sweeteners, including aspartame, and risk of common cancers. An exception was one study in Argentina that found a positive association between long-term use (≥10 y) of artificial sweeteners and risk of urinary tract tumors (UTT), compared to non-users; although for short-term users, no association was observed (Andreatta 2008).

The findings of two prospective cohort studies (Lim 2006; Schernhammer 2012) were not consistent. Lim et al. examined a large cohort of men and women from the NIH-AARP Diet and Health study and found no association between consumption of aspartame-containing beverages and risk of overall hematopoietic cancer, brain cancer, or their subtypes. A second large prospective cohort study involved the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) cohorts followed over 22 years with dietary intake measured every 4 years (Shernhammer 2013). In this study, the highest category of aspartame intake (≥143 mg/day from diet soda and packets) was associated with significantly elevated risk of non-Hodgkin lymphoma (NHL) and of multiple myeloma in men. Both of the prospective cohort studies that addressed cancer risk had limitations regarding generalizability. The NIH-AARP cohort had an age range of 50-71 years and was, therefore, not generalizable to the overall adult population. Additionally, the Panel did not consider the positive findings in Shernhammer et al. to be significant because the positive association between aspartame consumption and NHL was limited to men and lacked a clear dose-response relationship. Note: non-Hodgkin's lymphomas are ~49% of hematological malignancies in the US; myelomas are ~14%.

Further investigation should be considered to assure there is no association between aspartame consumption and specific cancer risk.

Preterm Delivery

Two European cohort studies were used in this evaluation. A large prospective cohort study (Halldorsson et al., 2010) from the Danish National Birth Cohort investigated associations between consumption of artificially sweetened and sugar sweetened soft drinks during pregnancy and subsequent pre-term delivery. Also, a large prospective cohort study of Norwegian women (Englund-Ögge et al., 2012) investigated the relationship between consumption of artificially sweetened and sugar sweetened soft drinks during the first 4-5 months of pregnancy and subsequent pre-term delivery. In addition, La Vecchia (2013) combined these two studies in a meta-analysis that was considered.

Regarding the Haldorsson study, significant trends in risk of pre-term delivery with increasing consumption of artificially sweetened drinks (carbonated and non-carbonated) were found, but not for sugar-sweetened drinks. In the highest exposure groups (≥ 4 serv/d) the odds ratios relative to non-consumption were 1.78 (95 % CI 1.19-2.66) and 1.29 (95 % CI 1.05-1.59) respectively for carbonated and noncarbonated artificially sweetened drinks. Associations with consumption of artificially sweetened carbonated drinks did not differ according to whether delivery was very early (< 32 weeks) or only moderately or late pre-term. The EFSA Panel noted that the prospective design and large size of the study sample were major strengths, and there were no important flaws in the methods used. The Panel agreed with the authors who concluded that replication of their findings in another setting was warranted.

Regarding the Englund-Ögge study, no significant trends were found in risk of pre-term delivery with increasing consumption of artificially sweetened drinks or sugar-sweetened drinks. Small elevations of risk were observed with higher consumption of artificially sweetened soft drinks, but after adjustment for covariates, these reached significance only when categories of consumption were aggregated to four levels, and then the odds ratio for the highest category (≥ 1 serving/day) was 1.11 (95 % CI 1.00-1.24) compared with non-consumption. This was driven by an increase in spontaneous but not medically induced pre-term delivery. Associations with sugar-sweetened soft drinks tended to be stronger, with an adjusted odds ratio of 1.25 (95 % CI 1.08-1.45) for consumption of at least 1 serv/d. The Panel noted that effects may have been underestimated because of inaccuracies in the assessment of dietary exposures, but the method was similar to that used by Halldorsson et al., and the same for sugar-sweetened as for artificially sweetened soft drinks.

Behavior and Cognition

Children

Two randomized controlled trials (RCTs) (Shaywitz 1994; Wolraich 1994) and two non-randomized controlled trials (Kruesi 1987; Roshon & Hagen 1989) conducted in the US were included in the evidence on effects of aspartame on behavior and cognition in children. Wolraich et al. compared diets high in sucrose to diets high in aspartame in 25 preschool and 23 primary school-age children and found that even when intake exceeded typical dietary levels, neither

dietary sucrose nor aspartame affected children's behavior or cognitive function. Shaywitz et al. examined the effect of large doses of aspartame (10 times usual consumption) on behavioral/cognitive function in children with attention deficit disorder (5-13 year of age) and found no effect of aspartame on cognitive, attentive, or behavioral testing. Roshon and Hagan examined 12 preschool children on alternate experimental days with a challenge of sucrose- or aspartame-containing drinks and found no significant differences in locomotion, task orientation or learning. Lastly, Kruesi et al. investigated the effect of sugar, aspartame, saccharin, and glucose on disruptive behavior in 30 preschool boys on four separate experimental days. There was no significant difference in scores of aggression or observer's ratings of behavior in response to any of the treatments. The limitations of this evidence were that all of the trials were approximately 20-30 years old, all had small sample sizes, and all were conducted over the short-term (1 day to 3 weeks). Overall, the Panel noted that no effects of aspartame on behavior and cognition were observed in children in these studies.

Adults

Seven studies on the effect of aspartame on adult behavior and cognition were included in this body of evidence. Five RCTs, one non-randomized controlled trial, and one case-control study were conducted in the US. Two of these trials examined a single experimental dose of aspartame on one day (Lapierre 1990; Ryan-Harshman 1987). Lapierre et al. examined 15 mg aspartame/kg body weight in 10 healthy adults and found no significant differences between aspartame and placebo in cognition or memory during the study. Ryan-Harshman et al. tested 13 healthy adult men and found no change in any behavioral effects measured. A third randomized crossover trial examined 48 adults over 20 days; half of the participants were given high dose aspartame (45 mg/kg/d) and half were given low dose aspartame (15 mg/kg/d) (Spiers 1998). This study found no neuropsychologic, neurophysiologic or behavioral effects linked to aspartame consumption. Two trials were conducted with pilots or college students to test cognitive abilities related to aviation tasks (Stokes 1991; Stokes 1993). In the first study, 12 pilots were given aspartame (50 mg/kg) or placebo and tested for aviation-related information processing after a single treatment on one day. There was no detection of performance decrements associated with exposure to aspartame. In the follow-up study, college students were given repeated dosing of aspartame (50 mg/kg for 9 days) and tested for aviation-related cognitive tasks. No impaired performance was observed. One non-randomized crossover trial examined the effects of aspartame on mood and well-being in 120 young college women and found no difference in changes in mood after consuming a 12 oz water or aspartame-sweetened beverage on a single day (Pivonka & Grunewald 1990). Lastly, a case-control study was conducted with 40 adults with unipolar depression and a similar number of subjects without a psychiatric history (Walton 1993). Participants were given aspartame (30 mg/kg) or placebo for 7 days and individuals with depression reported a difference in severity of self-scored symptoms between aspartame and placebo; whereas the non-depressed matched subjects reported no difference. This suggested that individuals with mood disorders may be sensitive to aspartame. Overall, the Panel noted the limited number of participants, the short duration of the studies, and the inconsistency of the reporting of the results in all adult studies. However, despite these limitations, the Panel concluded that there was no evidence that aspartame affects behavior or cognitive function in adults.

Other (Headaches, Seizures)

Several studies examined headaches and seizures. A number of RCTs were conducted to assess the incidence of headache after consumption of aspartame. One RCT tested the effects of aspartame within 24 hours of consumption (30 mg/kg) on 40 subjects with a history of headache and found no difference in the incidence rate of headaches (Schiffman 1987). Another RCT looked at the effect of aspartame on frequency and intensity of migraine headaches in 10 subjects with medical diagnosis of migraine headaches over 4 weeks (Koehler and Glaros, 1988). The authors found an increase in the frequency of migraine headaches with the aspartame treatment. In an RCT of 18 subjects with self-described sensitivity to aspartame, the participants reported headaches on 33% of the days, compared with 24% with placebo (Van den Eeden 1994). The authors concluded that a subset of the population may be susceptible to headaches induced by aspartame. Lastly, in a survey study of 171 patients at a headache unit, 8% reported that aspartame was a trigger of headaches compared to 2.3% for carbohydrates and 50% for alcohol (Lipton 1989). Overall, the Panel concluded the possible effect of aspartame on headaches had been investigated in various studies which reported conflicting results, ranging from no effect to the suggestion that a small subset of the population may be susceptible to aspartame-induced headaches. The number of existing studies was small and dated, and several studies had high dropout rates. The Panel noted that because of the limitations of the studies it was not possible to draw a conclusion on the relationship between aspartame consumption and headaches.

Several small studies assessed seizures. One RCT in children investigated whether aspartame would induce the occurrence of petit mal seizures (Camfield 1992). Ten children were given one treatment of aspartame at the ADI of 40 mg/kg and that treatment exacerbated the number of EEG spike waves per hour for these children without a history of seizures. In a second RCT, aspartame (34 mg/kg) was administered to 10 epileptic children over 2 weeks to examine the induction of seizures (Shaywitz 1994). No difference was found in the occurrence of seizures between aspartame and placebo exposure. Another RCT studied 18 subjects who claimed to have experienced epileptic seizures due to aspartame (Rowan 1995). One treatment (50 mg/kg) was administered on a single day and the authors reported no seizures or other adverse effect from aspartame treatment in this group. Overall, the Panel concluded that the available data do not provide evidence for a relationship between aspartame consumption and seizures.

Pregnancy Outcomes: Mode of Action (MoA) analysis

The EFSA Panel considered that adverse effects on reproduction and development reported for aspartame in animal studies could be attributed to the metabolite phenylalanine. They undertook a formal Mode of Action (MoA) analysis of the putative role of phenylalanine in developmental toxicity (as seen in animal studies).

Risk characterization was based on comparison of plasma phenylalanine levels following aspartame administration with plasma phenylalanine levels associated with developmental effects in children born from mothers with PKU. Current clinical practice guidelines recommend PKU patients restrict dietary intake of phenylalanine to keep plasma levels below 360μM. The

EFSA Panel noted that intakes of aspartame as a food additive could occur at the same time as other dietary phenylalanine sources. Therefore, they considered the threshold utilized for comparisons should be lowered to allow for simultaneous intake of aspartame with meals. So plasma phenylalanine from the diet (120μM) was subtracted from 360μM to determine the maximum safe plasma concentration of phenylalanine that can be derived from aspartame (240μM).

The Panel considered that given these conservative assumptions, realistic dietary intake of aspartame and the confidence intervals provided by the modeling, the peak plasma phenylalanine levels would not exceed the clinical target threshold of 240μM when a normal individual consumed aspartame at or below the current ADI of 40 mg/kg body weight/day. Therefore, the Panel concluded there would not be a risk of adverse effects on pregnancy in the general population at the current ADI.

For additional details on this body of evidence, visit: www.efsa.europa.eu/efsajournal

Table 1. Summary of Relevant Human Studies from the European Food Safety Authority (EFSA) Report: Scientific Opinion on the Re-evaluation of Aspartame as a Food Additive

Topic	Evidence	Outcomes	Strengths/ Limitations	Author Statements/ Other
Aspartame: Preterm Delivery	Large prospective cohort study (Halldorsson et al.) from the Danish National Birth Cohort investigated associations between consumption of artificially sweetened and sugar sweetened soft drinks during pregnancy and subsequent pre-term delivery.	Significant trends in risk of pre-term delivery with increasing consumption of artificially sweetened drinks (carbonated and non-carbonated), but not for sugar-sweetened drinks. For highest exposure groups (≥ 4 serv/d) vs non-consumption OR = 1.78 (95% CI 1.19-2.66) and 1.29 (95% CI 1.05-1.59) for carbonated and noncarbonated artificially sweetened drinks. Associations with consumption of artificially sweetened carbonated drinks did not differ according to whether delivery was very early (<32 weeks) or only moderately or late pre-term.	The Panel noted the prospective design and large size of study sample were major strengths, and there were no important flaws in the methods used. Panel agreed with the authors who concluded that replication of their findings in another setting was warranted.	Both Halldorsson and Englund-Ögge were well designed and conducted. Noting this, the Panel concluded that even at high levels of exposure to artificially sweetened soft drinks the risk of pre-term delivery is likely to be small, if any. The observed associations could be a consequence of uncontrolled residual confounding.
	Large prospective cohort study of Norwegian women (Englund-Ögge et al.) investigated the relationship between consumption of artificially sweetened and sugar-sweetened soft drinks during the first 4-5 months of pregnancy and subsequent pre-term delivery.	No significant trends were found in risk of pre-term delivery with increasing consumption of artificially sweetened drinks or sugar-sweetened drinks. Small elevations of risk were observed with higher consumption of artificially sweetened soft drinks, but after adjustment for covariates, these reached significance only when categories of consumption were aggregated to four levels, then OR = 1.11 (95% CI 1.00-1.24) for the highest category (≥ 1 serving/day) in comparison to non-consumption. This was driven by	The Panel noted that effects may have been underestimated because of non-differential inaccuracies in the assessment of dietary exposures, but the method was similar to that used by Halldorsson et al. and the same for sugar-sweetened as for artificially sweetened soft	

		an increase in spontaneous but not medically induced pre-term delivery. Associations with sugar-sweetened soft drinks tended to be stronger, with an adjusted OR = 1.25 (95% CI 1.08-1.45) for consumption of at least 1 serv/d.	drinks.	
	La Vecchia (2013) performed a meta-analysis of findings from Halldorsson et al. (2010) and Englund-Ögge et al.[20-22]	The analysis indicated similarly elevated risks of pre-term delivery with higher consumption both of sugar-sweetened and of artificially sweetened drinks.	The lack of specificity in the associations points to possible residual confounding.	
	Overall, currently available epidemiological data do not suggest that consumption of artificially sweetened soft drinks is a cause of pre-term delivery.			
Aspartame: Cancer	Case-control study (Hardell et.) in Sweden of 209 patients with brain tumors compared with 425 controls, selected from the Swedish Population Register and matched for sex, age and region of residence. The focus of study was exposure to ionizing radiation/cell phones, but information was also collected on consumption of low-calorie drinks, most of which contained aspartame.	Non-significant elevations of risk for consumption of low-calorie drinks in relation to brain tumors overall (OR = 1.24, 95% CI 0.72-2.14) and malignant brain tumors specifically (OR = 1.70, 95% CI 0.84-3.44).	The study had a high response rate, but was limited by its relatively small size, the basic assessment of exposure (low-calorie drinks), and the potential for recall bias (because cases knew that they had a brain tumor) all of which could have led to inflation of risk estimates.	
	Case-control study (Bunin et al.) of 315 US children with medulloblastoma/primitive neuroectodermal tumor diagnosed before the age of 6 y, and 315 control children (selected from the general population by random digit dialing).[24]	In an unadjusted analysis, a significant trend of increasing risk was observed with more frequent consumption of low-calorie carbonated drinks in the pre-conception period. This was attenuated after adjustment for potential confounders, with an adjusted OR = 1.3 (95% CI 0.7-2.5) for ≥2/day versus < 1/month. There were no significant associations with reported frequency of consuming diet soda during midpregnancy.	Assessment of exposure to diet soda required recall after an interval of several years and therefore may not have been reliable. It served only as a proxy for exposure to aspartame (at the time was the most widely used sweetener in soft drinks), and other possible sources of aspartame were	The authors concluded that their results generally did not support an association with aspartame, but the limitations, and also the low statistical power, restrict the conclusions that can be drawn from this study.

			not evaluated.	
	Linked set of case-control studies (Gallus et al.) in Italy assessed the association of artificial sweeteners with 9 types of cancer. Patients with incident, histologically confirmed cancers of the oral cavity and pharynx (598), esophagus (304), colon (1225), rectum (728), larynx (460), breast (2569), ovary (1031), prostate (1294) and kidney (767) were compared with 7028 controls admitted to the same hospitals for acute, non neoplastic disorders.	The ORs for consumption of other sweeteners, mainly aspartame, were 0.77 (95% CI 0.39–1.53) for cancers of the oral cavity and pharynx, 0.77 (95% CI 0.34–1.75) for esophageal, 0.90 (95% CI 0.70–1.16) for colon, 0.71 (95% CI 0.50–1.02) for rectal, 1.62 (95% CI 0.84–3.14) for laryngeal, 0.80 (95% CI 0.65–0.97) for breast, 0.75 (95% CI 0.56–1.00) for ovarian, 1.23 (95% CI 0.86–1.76) for prostate and 1.03 (95% CI 0.73–1.46) for kidney cancer. A significant inverse trend in risk for increasing categories of total sweeteners (incl saccharin) was found for breast and ovarian cancer, and a direct one for laryngeal cancer.	Misclassificatio n of exposures will have been non-differential (i.e. similar for cases and controls), in which case the effect will have been to bias risk estimates towards the null. Thus, while the results do not suggest a hazard for the cancers studied, on their own they provide only limited reassurance of safety.	The authors state this study provides no evidence that saccharin or other sweeteners (mainly aspartame) increase the risk of cancer at several common sites in humans.
	Case-control update of Gallus et al. in Italy (Bosetti et al.) to test possible associations of artificial sweeteners with 3 types of cancer. Cases were 230 patients with stomach cancer, 326 patients with pancreatic cancer and 454 patients with endometrial cancer. These were compared with 547, 652 and 908 controls, frequency matched by age, sex and study center.	ORs for use of low-calorie sweeteners versus non-use were 0.80 (95% CI, 0.45-1.43) for gastric cancer, 0.62 (95% CI, 0.37-1.04) for pancreatic cancer, and 0.96 (95%CI, 0.67-1.40) for endometrial cancer. Corresponding ORs for saccharin were 0.65 (95% CI, 0.25-1.68), 0.19 (95 % CI, 0.08-0.46), and 0.71 (95% CI, 0.36-1.38), and for other sweeteners were 0.86 (95% CI, 0.45-1.67), 1.16 (95%CI, 0.66-2.04), and 1.07 (95% CI, 0.71-1.61).	The findings do not suggest a hazard, but because exposures to aspartame specifically were not distinguished, and because of possible non-differential misclassificatio n of exposures, on their own they provide only limited evidence of safety.	Authors state that this study adds further evidence on the absence of an adverse effect of low-calorie sweeteners, including aspartame, on risk of common neoplasms.

	Case-control study (Andreatta et al.) in Argentina to investigate the relation between consumption of artificial sweeteners and urinary tract tumours (UTT). A study of 197 patients with incident confirmed transitional-cell UTTs along with 397 controls from the same area who had no history of cancer, and had been admitted to hospital with acute non-neoplastic, non-urinary tract diseases.	For long-term use (≥10 y) a positive association was found between use of artificial sweeteners and risk of UTT compared to non-users (OR = 2.18, 95% CI 1.22–3.89, adjusted for age, sex, BMI, social status, and years of tobacco use). For short-term consumers, no association with UTT was observed.	The Panel noted that ~80% of cases and controls who consumed artificial sweeteners, used saccharin or cyclamate. The study provided little information about possible risks from aspartame.	The authors concluded that use of artificial sweeteners for 10 years or more was positively associated with UTT.
	Prospective cohort study by Lim et al. from the NIH-AARP Diet and Health Study included 285,079 men and 188,905 women aged 50-71 y at entry, which was drawn from 8 areas in the US.[28] In this cohort, risk of hematopoietic cancer (1888 cases) and malignant glioma (315 cases) during 5 y follow-up (1995-2000) was examined in relation to daily intake of aspartame assessed at baseline.	During > 5 y follow-up, 1,888 hematopoietic cancers and 315 malignant gliomas. Higher levels of aspartame intake were not associated with the risk of overall hematopoietic cancer (RR for ≥600 mg/d = 0.98; 95% CI, 0.76-1.27), glioma (RR for ≥400 mg/d = 0.73; 95% CI, 0.46-1.15; P for inverse linear trend = 0.05), or their subtypes in men and women.	The Panel noted that major strengths of this investigation were its prospective longitudinal design, large number of cases, and that exposures were assessed at baseline and therefore unbiased by knowledge of disease outcome. Ascertainment of cancers was reliable. Confounding was unlikely to have been a major problem, although there was no adjustment for socio-economic status (which has shown some relation with brain cancer). Assessment of exposure to aspartame covered aspartame containing drinks as well as addition of aspartame to coffee and tea, but it was limited to one point in time, and usage in	The authors concluded that their prospective study suggested that aspartame consumption derived from its main source, aspartame-containing beverages, does not raise the risk of hematopoietic or brain malignancies.

			the years before the study may have been lower.	
	Pilot case-control study (Cabaniols et al.) conducted in France to investigate lifestyle factors and brain cancer risk with 122 incident adult cases of malignant primitive brain tumors (MPBT) and 122 controls with other neurological diagnoses.	There was no association between aspartame consumption during the past five years of at least once per week and risk of MPBT (OR = 1.02, 95% CI 0.57-1.85).	Information on the method of dietary assessment was limited, and there was no attempt to control for potential confounding other than sex and age. In view of this, and the low statistical power of the study (reflected in the CI), the nonpositive finding provides little reassurance of an absence of hazard.	The authors stated that additional large clinical studies are needed to confirm these findings.

	Prospective cohort study with Nurses' Health Study and Health Professionals Follow-Up Study cohorts (Schernhammer et al.).[30] The risk of lymphatic and hematopoietic cancers in relation to consumption of diet soda and aspartame sweeteners added at the table was examined; 77,218 female registered nurses and 47,810 male health professionals were followed for 22 y.	1,324 subjects developed non-Hodgkin lymphoma (NHL), 285 multiple myeloma, and 339 leukemia (mostly myeloid leukemia). The highest category of aspartame intake (≥143 mg/day) was associated with elevated relative risk of NHL (RR = 1.64, 95% CI 1.17-2.29) and of multiple myeloma (RR = 3.36, 95% CI 1.38-8.19) in men. There was no consistent trend in risk with increasing exposure, and there were no corresponding elevations in risk in women. No clear association with leukemia was apparent in either men or women.	Major strengths of this study were its prospective design, the substantial number of cancer cases, the repeated assessment of dietary intake every 4 y, aspartame intake assessed from time of entry in US diet, and many potential confounders assessed. The Panel stated that the positive findings can be given little weight, given their limitation to men, the small relative risks observed, and the lack of clear dose-response relationships.	Schernhammer et al speculated that the differential findings for men and women might reflect differences in the activity of alcohol dehydrogenase type 1, which converts methanol (a metabolite of aspartame) to formaldehyde, and is higher in men than in women.
	The Panel considered that the results of these epidemiological studies do not suggest an increased risk associated with aspartame consumption for the types of cancer examined.			
Aspartame: Metabolic Outcomes	Randomized controlled trial (Leon et al. 1989) on the effects of aspartame on metabolic outcomes.[31] Participants included 57 women and 51 men randomly assigned to either the aspartame (n = 53, 75 mg/kg/d) or placebo (n = 55) for 24 wks.	No treatment-related hematological changes, alterations in clinical chemistry, urinary abnormalities, or differences in vital signs or body weight. No differences in blood formate or methanol; urinary Ca2+ or formate; serum folate; or serum lipids. No significant changes in amino acid profiles and no evidence of accumulation of phenylalanine or tyrosine.		
	Controlled diet study (Porikos and Van Italie) with 21 men (24-45 y) given a baseline diet (25-30 % calories from sucrose) alternating with a calorie restricted diet (sweetness replaced with aspartame).	There were small increases in blood urea nitrogen (BUN) in subjects on aspartame containing diet, but renal function remained within normal parameters. Serum triglycerides decreased by 33 % on the aspartame diet.	The Panel noted that the dose of aspartame was not specified and that there were other changes in the diet, including changes in its caloric content.	
	Overall, the Panel concluded that no significant adverse effects were observed following repeated administration of aspartame for different durations and at different dose levels of aspartame in healthy subjects.			

Aspartame: Behavior and Cognition Children	Cross-over study (Kruesi et al.) investigated the effect of sugar and aspartame consumption on behavior in 30 preschool boys (2 - 6 y).[33] Double blind cross-over challenge with aspartame (30 mg/kg bw), sucrose (1.75 g/kg bw), saccharin (amount not specified) and glucose (1.75 g/kg bw).	There was no significant difference in scores of aggression or observers'' ratings of behavior between the sugar responsive and age-matched control boys following any of the four treatments.		
	Randomized cross-over trial (Wolraich et al.) with 25 normal preschool children (3 - 5 y) and 23 primary school-age children (6 - 10 y). Over three consecutive 3-wk periods, double blind randomized distribution to a diet high in aspartame (32-38 mg/kg/d), sucrose (4500-5600 mg/kg/d), or saccharin (10-12 mg/kg/d).	For the children described as sugar-sensitive, there were no significant differences among the 3 diets in any of the 39 behavioral and cognitive variables. For the preschool children significant differences were measured in 4 of the 31 measures (Parents'' ratings of cognition, grooved pegboard, dominant hand, non-dominant hand); however, no consistent pattern in behavioral and cognitive differences was observed amongst the 3 diets.		The authors concluded that 'even when intake exceeded typical dietary levels, neither dietary sucrose nor aspartame affects children's behavior or cognitive function'.
	Randomized crossover trial (Shaywitz et al.) of the effect of large doses of aspartame on behavior, cognitive function and monoamine metabolism in 15 children with attention deficit disorder (11 boys and 4 girls, 5-13 y). The trial consisted of two 2-week periods that were identical except for the administration of either aspartame (34 mg/kg/d) or placebo (microcrystalline cellulose).	No significant effect of aspartame on cognitive, attentive or behavioral testing. The biochemical and hematological parameters were not altered by aspartame except that plasma phenylalanine levels increased by approximately 40 % two hours following aspartame administration (within in normal postprandial range).		The authors state that the findings indicate that aspartame at greater than 10 times usual consumption had no effect on the cognitive and behavioral status of children with attention deficit disorder. In addition, aspartame did not appear to affect urinary excretion rates of monoamines and metabolites.
	Non-randomized, controlled study of Roshon and Hagen (1989) examined the effect of sucrose consumption on the behavior of 12 preschool children (6 boys and 6 girls, 3-5 y).	No significant difference in locomotion, task orientation and learning in participants exposed to either sucrose or placebo (9 mg aspartame/kg).		
	The Panel noted that no effects of aspartame on behavior and cognition were observed in children in these studies.			
Aspartame: Behavior and Cognition Adults	Randomized, crossover trial (Lapierre et al.) with 10 healthy adults (6 men, 4 women, 21—36 y) who received a single dose of aspartame (15 mg/kg) or placebo capsules.	No significant differences between aspartame and placebo were found in measures of sedation, hunger, headache, reaction-time, cognition or memory during the study. Plasma phenylalanine levels rose within thirty minutes of administration of aspartame.		

	Randomized crossover trial (Ryan-Harshman et al.) with healthy males age 20 - 35 y (n = 13/group) given phenylalanine capsules (0.8, 2.5, 5 and 10 g) or aspartame (5 or 10 g) as a single dose to investigate neurobehavioral effects on energy and macronutrient selection and on subjective feelings of hunger, mood and arousal.	Neither phenylalanine nor aspartame altered mean energy intakes or macronutrient selection nor caused any behavioral effects.		
	Non-randomized, controlled crossover study (Pivonka and Grunewald 1990) examined the effect on mood and well-being in 120 women (18 - 30 y) receiving water, aspartame-sweetened or sugar-sweetened beverages.	Mood tests employed were the Stanford Sleepiness Scale (SSS), the Visual Analogue Mood Scale (VAMS), and the Profile of Mood States (POMS). Changes in mood were similar following consumption of water or the aspartame-sweetened beverage. However, the ingestion of the sugar-sweetened beverage was followed by increased sleepiness during the last half of the one-hour observation period (p less than .002).		
	Double-blind study (Stokes et al.), 12 healthy pilots (4 females and 8 males) were given placebo, aspartame (50 mg/kg bw) or ethanol (positive control, dose not reported but estimated to raise plasma alcohol to 0.1 %).[40] Each subject performed the SPARTANS cognitive test battery of aviation-relevant information-processing tasks on 5 sessions after a single treatment.	No detectable performance decrements were associated with the exposure to aspartame, but decrements in psychomotor and spatial abilities were detected following ethanol administration.		
	Follow up study (Stokes et al.) was undertaken in 12 subjects (college students, sex not reported) in order to examine the effects of double-blind repeated dosing of aspartame on performance in aviation-relevant cognitive tasks. The subjects received placebo capsules or aspartame capsules (50 mg/kg bw/day) for 9 days, or an acute dose of ethanol to achieve 0.1 % blood ethanol levels.	Forty-seven task variables were measured using the SPARTANS 2.0 cognitive test battery and no significantly impaired performance on flight-relevant cognitive tasks was observed.		

	Study by Walton et al. was designed to test whether subjects with mood disorders were sensitive to adverse effects caused by aspartame; 40 adult patients with unipolar depression and a similar number of adult subjects without a psychiatric history were recruited. The participants were given aspartame (30 mg/kg bw/day) or placebo (sucrose) in capsules for a period of 7 days with two 3-day washout periods using a double-blind cross-over study design.	Despite the small number of subjects, there was a significant difference in the number and severity of self-scored symptoms between aspartame and placebo in the patient group while there was no difference in the non-depressed volunteer group.		
	Randomized double-blind placebo-controlled 3-way crossover, 48 adults (24 men, 24 women, 18—34 y) were exposed after an initial one-month aspartame-free period, to aspartame, sucrose or placebo administered for 20 days each (Spiers et al.).[43] Twenty-four participants were given a high dose of aspartame (45 mg/kg/d) and the remaining received a low dose of aspartame (15 mg/kg/d). The dose of sucrose was 90 g/day for all subjects. Administration of aspartame or placebo (microcrystalline cellulose) was in the form of capsules and for sucrose, a beverage.	Plasma phenylalanine levels increased dose-dependently with aspartame consumption from 56 μM (placebo) to 79 μM (high dose), but no neuropsychologic, neurophysiologic and behavioral effects linked to aspartame consumption were observed.		
	The Panel noted the limited number of participants, the short duration and the inconsistency of the reporting of the results in all these adult human studies. These limitations apply to both positive and negative studies. Overall, the Panel concluded that there was no evidence that aspartame affects behavior or cognitive function in children or adults.			
Aspartame: Seizures	Double-blind study in 8 girls and 2 boys (5.1 - 14.6 y) diagnosed with generalized absence seizures (petit mal seizures) to investigate whether aspartame exacerbates occurrence of seizures (Camfield et al.).[44] Following 1-hr baseline recordings of the number and length of spike-wave bursts (determined using an ambulatory cassette EEG recorder), the children were given 250 ml orange juice sweetened with either aspartame (40 mg/kg) or sucrose (1 g sucrose for every 25 mg aspartame to achieve	Following the consumption of aspartame but not of sucrose, the total duration of spike-wave discharge per hr was significantly increased and aspartame appeared to exacerbate the amount of EEG spike waves in children with absence seizures.	The Panel noted that the combination of the two parameters (number and length of spike-wave bursts) into a single measure was not adequately explained, and lack of control of food and drink intake before and after dosing may have affected the results. The Panel further noted that aspartame was	

	similar sweetness) (assigned randomly) and the EEG recordings were continued for 6 h. Each child was tested once with each substance.		given in a single dose at the ADI.	
	Randomized double-blind placebo-controlled, crossover study (Shaywitz et al.) aspartame (34 mg/kg) was administered to epileptic children (5 boys, 5 girls, 5-13 y) for 2 wks to investigate the induction of seizures following aspartame consumption.	Nine children completed the study and it was reported that there was no difference in the occurrence of seizures between aspartame and placebo exposure. The plasma levels of phenylalanine increased from 60 μM to 82 μM by one hour post aspartame administration.		
	Randomized double-blind placebo-controlled crossover study by Rowan et al.[46] In this trial, subjects (sixteen adults and two children) who claimed to have experienced epileptic seizures reportedly due to aspartame were given capsules either containing microcrystalline cellulose (placebo) or aspartame (total dose of 50 mg/kg bw). This dose was divided into three portions and administered in the morning at two-hour intervals	The authors reported no seizures or other adverse effects from aspartame ingestion. Mean plasma phenylalanine levels increased from 52 μM (after placebo) to 84 μM two hours after the first two doses aspartame.		
	Overall the Panel concluded that the available data do not provide evidence for a relationship between aspartame consumption and seizures.			
Aspartame: Headaches	Schiffman et al. reported a randomized double-blind crossover trial with aspartame on 40 subjects with a history of headache and related neurologic symptoms within 24h of aspartame consumption.[47] The subjects (12 males and 28 females, 19—69 y) were given aspartame (30 mg/kg bw) or placebo (microcrystalline cellulose) in capsules; the dose was divided into 3 doses administered in the morning at 2 h intervals.	The incidence rate of headache after consumption of aspartame (35%) was not significantly different from that after placebo (45%).		

	Randomized cross-over trial by Koehler and Glaros comparing the effect of aspartame to matched placebo on frequency and intensity of migraine headache.[48] The subjects (2 males, 8 females; 18 - 47 y) who had medical diagnosis of migraine, consumed aspartame (1200 mg/person) or placebo (microcrystalline cellulose) in capsules and during two 4 wk phases.	Statistical analysis indicated a significant increase in the frequency of migraine headaches from the placebo to the aspartame treatment (mean number of migraines per subject: 1.72 (baseline phase), 1.55 (placebo phase), and 3.55 (aspartame phase)). No differences were reported in the intensity or duration of migraine headaches.	The high drop-out rate, from 25 to 11 participants in this study was not due to increased frequency or intensity of migraines. The Panel noted that the high inter individual variability in the response of the remaining volunteers makes interpretation unreliable.	
	In the study by Lipton et al. 171 patients at a headache unit completed a survey in which alcohol, aspartame, or carbohydrates intake were felt to be triggers of their headaches.	Study showed that 8% reported aspartame as a trigger of headaches compared to 2.3% for carbohydrates, and to about 50% for alcohol.	The Panel considered that having only listed possible triggers of headaches was a major limitation of this study.	
	Van den Eeden et al. conducted a double-blind randomized cross-over trial with subjects self-diagnosed as sensitive to aspartame.[50] Of the 32 subjects recruited and randomized to receive aspartame (in capsules given 3X/d to give a daily dose of 30 mg/kg bw/day for 7 d) and placebo (microcrystalline cellulose in capsules given 3X/d), only 18 participants completed the full study.	Participants reported headaches on 33 % of days during aspartame intake, compared with 24 % on placebo treatment ($p = 0.04$). However, no significant difference in the length or intensity of headaches or in the occurrence of side effects associated with the headaches was observed between treatments.		The authors concluded that a small subset of the population may be susceptible to headaches induced by aspartame.
	The possible effect of aspartame on headaches has been investigated in various studies, which reported conflicting results, ranging from no effect to the suggestion that a small subset of the population may be susceptible to aspartame-induced headaches. The number of existing studies was small, and several had high participant drop-out rates, both under placebo and aspartame treatment. Overall, the Panel noted that because of the limitations of the studies it is not possible to conclude on a relationship between aspartame consumption and headaches.			
Aspartame: Eating Behavior	The Panel is aware that a number of studies have focused on the effects of aspartame on appetite, hunger and food intake. The Panel considered that these studies of the effect of aspartame (or other low calorie sweeteners) on eating behavior were not relevant for the assessment of the safety of aspartame and that risk benefit assessment of aspartame are not within the term of reference and the remit of the Panel.			

Aspartame: Allergenicity	Study by Szucs et al. on aspartame effects on mast cells in vitro.	Aspartame did not affect IgE-mediated histamine release from mast cells in vitro. Mast cells cultured in the presence of aspartame for up to 9 days showed enhanced proliferation and decreased responsiveness to releasing stimuli.	The authors concluded that the effect of aspartame on proliferation of cells in culture could be ascribed to a nonspecific enhancing effect of its constituent amino acids. Aspartame did not stimulate mast cell or basophil in vivo as assessed by skin testing.	
	Kulczycki reported a cases of aspartame induced urticaria.	Reported a case of aspartame induced urticaria confirmed by double blind challenge in a 23 year old woman with no history of allergic disease. A second case in a 42 year old woman was also reported.		
	Garriga et al. (1991) attempted to identify subjects with hypersensitivity reactions to aspartame with blinded challenge procedures.[53] A total of 61 self-referrals and physician referrals were screened, with 20 referrals evaluated in the clinic. Twelve patients underwent single- and double-blind challenge with up to 2000 mg of aspartame.	No subject with a clearly reproducible adverse reaction to aspartame was identified.	The authors concluded that subjects who believed themselves to be allergic to aspartame did not have reproducible reactions.	
	Geha et al. conducted a multi-centre placebo-controlled clinical study to evaluate individuals who had experienced urticaria and/or angioedema associated with ingestion of food containing aspartame.[54] In a double-blind crossover study, 21 recruited subjects with a self-reported history of hypersensitivity to aspartame were exposed to aspartame and placebo. Conversion products of aspartame, aspartyl-phenylalanine diketopiperazine and beta-aspartame, were also included in the study. Patients received, on different days, increasing doses of aspartame (50, 300, 600 mg) and	Four urticaria reactions were observed, two followed aspartame ingestion and two followed placebo ingestion.	The authors concluded that aspartame and its conversion products were no more likely than placebo to cause allergic symptoms in subjects with a history consistent with hypersensitivity to aspartame.	

	placebo.			
	Butchko et al. reviewed all published papers from 1980 onwards reporting allergic-type reactions and attributed to aspartame exposure.	In an evaluation of consumer complaints related to aspartame by the Centers for Disease Control and Prevention (CDC, 1984) approximately 15 % of the anecdotal complaints were assigned to allergic-dermatologic reactions attributed to aspartame ingestion, such as rashes, sore throat/mouth, swelling and itching. Cases of urticaria and granulomatous panniculitis thought to be related to aspartame were reported.		
	The Panel noted that the studies available were performed on a limited number of participants. Overall, taking into account the limited data currently available, the Panel considered that the weight of evidence does not suggest that aspartame is associated with allergic-type reactions in experimental models or in humans. However, the Panel cannot exclude the possibility that in rare instances individuals could be susceptible to allergic reactions following aspartame ingestion.			
Aspartame: Allergies in Children	Prospective cohort study by Maslova et al. explored how intake of artificially sweetened beverages during pregnancy related to asthma and allergic rhinitis in children at 18 months and 7 years of age.[56] Analysis was based on 60,466 pregnant women who enrolled in the prospective longitudinal Danish National Birth Cohort between 1996 and 2002.	In comparison with no consumption of artificially sweetened non-carbonated soft drinks during pregnancy, consumption of at least one serving per day was associated with an increased risk of asthma by three of the four case definitions (odds ratios up to 1.23, 95% CI 1.13-1.33 for asthma at 18 months), but there was no consistent exposure-response relationship across lower frequencies of consumption. In a corresponding analysis for artificially sweetened carbonated soft drinks, elevated odds ratios were observed for all four case definitions with the highest odds ratios of 1.30, 95% CI 1.01 — 1.66 for asthma at 7 years of age identified through the Danish National Patient Registry, but again without clear exposure-response relationships. Allergic rhinitis was non-significantly associated with daily consumption of artificially sweetened carbonated soft drinks (OR 1.31, 95% CI 0.98-1.74); no association was observed with daily consumption of artificially sweetened non-carbonated drinks (odds ratios of 1.03, 95% CI 0.86-1.24).	Because in epidemiological terms, the elevations of risk were only small and inconsistent, the findings from this study can only be considered weakly suggestive of hazard i.e. an association between the consumption of artificially sweetened beverages during pregnancy and the diagnosis of asthma or allergic rhinitis in children. Before a final conclusion can be reached with regard to aspartame, the findings need to be explored further with more detailed assessment of exposure to specific artificial sweeteners.	
Mode of Action (MoA)	The Panel considered that adverse effects on reproduction and development reported for aspartame in animal studies could be attributed to the metabolite phenylalanine. They undertook a formal Mode of Action (MoA) analysis of the putative role of phenylalanine in developmental toxicity (as seen in animal studies).[19]			

	Risk characterization was based on comparison of plasma phenylalanine levels following aspartame administration with plasma phenylalanine levels associated with developmental effects in children born from mothers with PKU. Data on the concentrations of phenylalanine in plasma after different doses of aspartame were extracted from various studies, mainly unpublished studies submitted in response to EFSA's call for data.	Current clinical practice guidelines recommend PKU patients restrict dietary intake of phenylalanine to keep plasma levels below 360 µM. The Panel noted that intakes of aspartame as a food additive could occur at the same time as other dietary phenylalanine sources. Therefore, they considered the threshold utilized for comparisons should be lowered to allow for simultaneous intake of the food additive with meals. The highest mean dietary phenylalanine exposure per meal is 34.2 mg/kg bw and this corresponds to a phenylalanine plasma concentration of 120 µM. So plasma phenylalanine from the diet (120 µM) was subtracted from 360 µM to determine the maximum safe plasma concentration of phenylalanine that can be derived from aspartame (240 µM).	The Panel considered that given the conservative assumptions, realistic dietary intake of aspartame and the confidence intervals provided by the modeling, the peak plasma phenylalanine levels would not exceed the clinical target threshold when a normal individual consumed aspartame at levels below the current ADI of 40 mg/kg bw/day.	The Panel therefore concluded that there would not be a risk of adverse effects on pregnancy in the general population including heterozygous individuals at the current ADI.

Overall Conclusions

The Panel concluded that chronic toxicity and reproductive and developmental toxicity were the critical endpoints in the animal database. The Panel considered that the evaluation of long-term effects of aspartame should continue to be based on the animal data. Based on a Mode of Action analysis and the weight-of-evidence, the Panel considered that the reproductive and developmental toxicity in animals was due to phenylalanine released from aspartame and concluded that the basis for evaluation of the reproductive and developmental endpoint should be the available data in humans.

Conservative estimates of exposure to aspartame made by the Panel for the general population were ≤36 mg/kg bw/day at the 95th percentile.

Due to the conservatism of both the exposure assessment and the aspartame dose-phenylalanine concentration response modeling, the Panel considered that it was highly unlikely that any individual in the normal and PKU heterozygous population would have plasma levels of phenylalanine above 240 uM following oral aspartame exposure up to the ADI of 40mg/kg bw/day. The Panel further considered that even in combination with diet, these aspartame intakes would not lead to peak plasma phenylalanine concentrations above 360 uM, the current clinical guideline for prevention of adverse effects on the fetuses of PKU mothers.

The Panel concluded from the present assessment of aspartame that there were no safety concerns at the current ADI of 40 mg/kg bw/day. Therefore, there was no reason to revise the ADI for aspartame.

The Panel emphasized that its evaluation of phenylalanine plasma levels from a dose of aspartame at the ensuing ADI is not applicable to PKU patients. These individuals require total control of dietary phenylalanine intake to manage the risk from elevated phenylalanine plasma levels.

Research Recommendations

1. Examine the risks of aspartame related to some cancers, especially hematopoietic ones, and pregnancy outcomes.

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