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# **Safety of Aspartame: A Review of Human Studies**

**Author: Manuel Attard**  
**Supervisor: Prof. Christine Edwards**

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## **INTRODUCTION**

### **Properties, Uses and Consumption**

Aspartame, an artificial non-nutritive sweetener, is a methyl ester of the dipeptide of the amino acids L-aspartic acid and L-phenylalanine. It is a white crystalline powder approximately 200 times sweeter than sucrose. Aspartame was discovered in 1965 and granted initial marketing authorisation in 1974. Permission to use in solid food was granted by the Food and Drug Administration (FDA) in 1981, extended to soft drinks in 1983 and for use as a general sweetener in 1996.

Aspartame is now found in approximately 6,000 consumer foods and beverages sold worldwide, mainly in the United States and Europe, with varying aspartame content as shown in Table 1 (Butchko & Stragel, 2001). As with other sugar substitutes, aspartame is used to assist in weight loss: by replacing high-energy sugars or corn syrups with a sweetener having practically no food energy; for dental care, since artificial sweeteners are not fermented by the microflora and so do not contribute to plaque formation; and in diabetics since artificial sweeteners do not cause insulin responses.

In humans, aspartame is completely metabolised in the gastrointestinal tract into phenylalanine (50%), aspartic acid (40%) and methanol (10%) before entering the circulation, as shown in Figure 1 (Stegink et al., 1987). Due to the phenylalanine produced, phenylketonurics should avoid it; moreover it should not be used in cooking and baking as it degrades at high temperatures (Conceicao et al., 2005).

**Table 1. Approximate aspartame content of some foods and beverages. Source: Butchko and Stagel (2001)**

Food	Serving size	Aspartame content (mg)
Beverage	355mL	180
Yogurt	240mL	125
Hot chocolate	180mL	50
Tabletop sweetener	1 packet	35
Pudding dessert	120mL	25

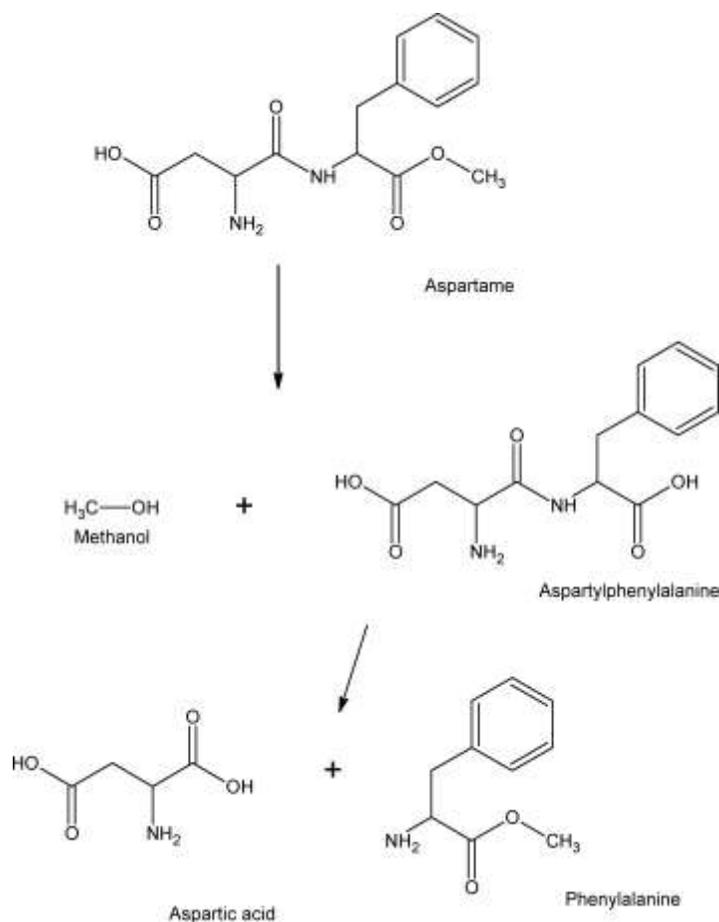


Figure 1. Metabolism of Aspartame. Source: Magnuson et al. (2007)

The acceptable daily intake (ADI) of aspartame is set at 40mg/kg of bodyweight (bw) by the European Union Scientific Committee (JECFA, 1980) while the U.S. FDA set the ADI at 50mg/kg bw (FDA, 1984). For a typical 70 kilogram adult, the FDA’s ADI will be equivalent to 3,500 mg of aspartame per day which translates to an intake of 19 cans of diet soft drink each day or 100 packets of tabletop sweetener, far more than most adults typically consume. A 30kg child would have to drink more than 8 cans of diet soft drink each day before reaching the ADI of aspartame. Several studies have estimated the consumption of aspartame worldwide and on average, intake of aspartame was below 3mg/kg bw per person per day and the intake for the 95<sup>th</sup> percentile of consumers was below 8 mg/kg bw per day (Magnuson et al., 2007).

## **The Aspartame Controversy**

Since its approval by the FDA in 1974, aspartame has been the subject of several controversies, scares and hoaxes. Indeed, if “aspartame” is searched in any internet search engine, the vast majority of pages found will be advising against its use and reporting how this sweetener is the cause of a variety of ailments ranging from headaches, depression and seizures to cancers, birth defects and death. The controversy originated during the 1970s about alleged conflicts of interest in its approval and allegations that aspartame producer G.D. Searle had withheld safety data. Marketing authorisation was subsequently suspended, however following a reassessment of the studies together with supporting new data, the FDA regranted approval in 1981.

In 1996 concerns about the safety of aspartame were rekindled by Olney et al. (1996) in a report suggesting that aspartame was the cause of the increasing brain tumours in the United States. This report, and the general public’s concern about the sweetener, lead the Scientific Committee on Food (SCF) to reinvestigate the data and after reviewing more than 500 scientific papers published between 1988 and 2001, pertaining to the safety of aspartame, the SCF concluded that there was no evidence that the sweetener was linked to any adverse effects (EC, 2002).

Yet, despite health authorities’ strong belief that aspartame is completely safe, consumer concerns have lead to supermarket chains Sainsbury (Daily Mail, 2007a), Asda (Daily Mail, 2007b), M&S (Daily Telegraph, 2007), and Woolworths (Food Stuff South Africa, 2009) to recently stop using aspartame in their own label products. In 2010 the British Food Standards Agency has launched a new study investigating possible health effects of the sweetener (Food Standards Agency, 2009).

While animal studies have an important role to play in the investigation of the safety aspects of aspartame, extrapolation to humans is not always reliable due to differences in physiology and metabolism. Moreover, when one is looking at data from animal studies utilising massive doses, one should keep in mind that “*all substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy*” –Paracelsus (1493-1541). This review will

thus focus on human studies; by discussing all eligible human studies published to date a conclusion will be drawn on whether there is actually cause for concern in the use of aspartame.

## **METHODS**

A literature search to identify human studies investigating the safety of aspartame was conducted by searching in both PubMed and The Cochrane Library with keywords aspartame AND [health OR safety OR toxicity OR adverse OR methanol OR formaldehyde OR formic acid OR diketopiperazine OR cancers OR tumours OR headaches OR migraines OR behaviour OR mood OR cognition OR brain OR seizures]. Manual searching of the reference lists in each relevant paper was also done to identify any missed papers. Inclusion criteria were full-text peer-reviewed human studies in the English language. Exclusion criteria were case studies, intervention studies not using a control and studies in animals, however some relevant animal studies will be referred to in the text to set the background against which the human studies were conducted. Studies in phenylketonurics were also excluded since people with this condition are unable to metabolize phenylalanine properly from any source and hence have to avoid any food or beverage containing significant amounts of phenylalanine, including aspartame. Evidence tables were constructed for each section to provide a summary of the data reviewed.

## **ASPARTAME AND HEALTH CONCERNS**

### **General**

Acute studies in mice, rats and rabbits using oral doses of aspartame as high as 10g/kg bw have recorded no deaths or adverse effects (Magnuson et al., 2007). Subchronic studies with doses up to 13, 10 or 6g/kg bw/day in mice, rats and dogs respectively also found no adverse effects resulting from aspartame consumption (Magnuson et al., 2007).

An early human study on the safety of aspartame was carried out in 1976 by Frey, involving 126 children and young adults aged 2 to 21 years. The study was a double-blind randomized control trial where the participants received either aspartame (at doses of 27-77mg/kg bw/day) or sucrose for 13 weeks. A physical and ophthalmoscopic examination, together with measurements of blood amino acids and methanol measurements, blood counts and urine analysis were carried out before and after treatment; no changes were recorded.

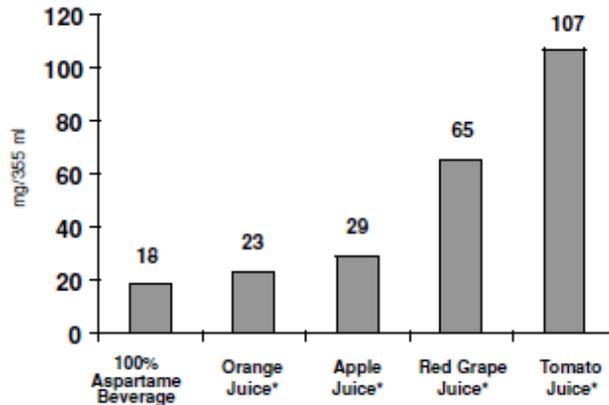
A similar study was carried out by Leon et al. (1989). This was a randomized, controlled, double-blind trial involving 108 healthy volunteers between 18 and 62 years old. 53 participants were given 900mg aspartame a day while 55 (the placebo group) were given microcrystalline cellulose for 24 weeks. Both were supplied in capsules (3 capsules a day). Extensive clinical and biochemical measurements were taken at baseline and after 3, 6, 9, 12, 18 and 24 weeks. During weeks 3 and 24, plasma tyrosine levels were higher in the group consuming aspartame, however they were still within normal ranges. There were no changes in any of the other parameters, nor were there any statistical differences in complaints including headaches.

A study by Walton et al. (1993) was designed to investigate whether individuals with mood disorders were more susceptible to adverse effects by aspartame. Subjects were adults between 24-60 years old undergoing treatment for depression (3 men and 5 women) and nondepressed controls (3 men and 2 females) of which 3 reported being sensitive to aspartame. The study had a cross-over design, and subjects received either 30mg/kg bw/day of aspartame or placebo for 7 days, with 3 days of washout. The study had to be halted after a total 8 individuals with unipolar

depression had completed the study due to the severity of the reactions within this group of patients (one subject suffered from retinal detachment and another experienced a conjunctival haemorrhage during her aspartame week). While the incidence of adverse effects between placebo and aspartame treatments was not significant in nondepressed subjects (total of 5 subjects), in subjects with a history of depression, the incidence of adverse reactions (mainly nausea, headaches and depression) between the aspartame and placebo treatments were significant ( $p < 0.01$ ). The authors thus suggest that further studies should be undertaken to evaluate the safety of the sweetener.

### **Methanol and Other Metabolic and Degradation Products**

As one of the metabolites of aspartame is methanol, it has been purported that this compound is the cause of aspartame's alleged adverse effects. In the liver, methanol is metabolized to formaldehyde which is rapidly converted to formic acid. At high doses of methanol, formic acid accumulation is known to induce metabolic acidosis (Barceloux et al., 2002). The lowest blood methanol concentration reported to be associated with these effects is 126mg/dl (Kostic & Dart, 2003). In a study with 30 healthy adults, it was shown that at doses of aspartame of 34mg/kg bw, no methanol was detectable in the blood; at 100mg/kg bw, methanol levels peaked at 1.27 mg/dl and at 200mg/kg bw, blood methanol levels peaked at 2.58 mg/dl (Stegink et al., 1981). The authors reported that at all doses, formate levels remained below the limits of detection. The same author conducted a similar study in one-year old infants and found that at aspartame intake of 34 and 50mg/kg bw/day, methanol levels remained below the limits of detection while at 100mg/kg bw/day, methanol levels peaked at 1.02mg/dl (Stegnik et al., 1983). Thus, blood methanol levels after ingestion of up to twice the ADI for aspartame, remain well below the level at which metabolic acidosis occurs. It should also be pointed out that methanol is found in a large number of natural foods (Maher & Wurtman, 1983) and in some is found at considerably higher levels than the amounts which would be generated by normal aspartame consumption, as can be seen in Figure 2.



**Figure 2. Methanol derived from aspartame in a 100% aspartame-sweetened beverage compared to that derived from various fruit juices. Source: Wucherpfennig et al. (1983)**

The other direct metabolic products of aspartame are phenylalanine and aspartic acid. The former will be discussed in a later section (*Effects on behaviour, mood and cognitive function*). Aspartic acid, while being an excitotoxin (a substance that damages neurons through overstimulation of brain and nerve cells) at high concentrations, is unable to cross the blood-brain barrier in most parts of the brain (Smith, 2000). Moreover, it is known that humans are not as susceptible to excitotoxins as rodents and hence conclusions cannot be made about human safety from excitotoxin response in rodent studies (Reynolds et al., 1976). Furthermore, it has been demonstrated that there is no significant increase in plasma aspartic acid following oral administration of aspartame at a dose of 34mg/kg bw (Stegnik & Filer, 1984).

Another concern regards diketopiperazine (DKP), a degradation product of aspartame. It has been found that after 6 months, 25% of the aspartame in beverages is converted to DKP (Tsang et al., 1985). DKP has been shown to be neither genotoxic nor carcinogenic in rats and mice (AFSSA, 2002). Only one human study involving the administration of DKP was identified (Geha et al., 1993). Participants of this study were 21 individuals who reported suffering adverse effects following consumption of aspartame. The study was a randomized, controlled, double blind cross-over study giving the participants either capsules containing 950mg of aspartame, 15mg of DKP and 7.5mg  $\beta$ -aspartame (another possible breakdown product of aspartame) or placebo. Each treatment lasted for a day and there was a 1 day washout between treatments. It was shown that aspartame and its breakdown products DKP and  $\beta$ -aspartame, were no more likely to cause adverse effects than placebo.

## **Cancer**

Taking into account all animal studies performed up to 2002, the French Agency of Medical Security for Food concluded that aspartame had no carcinogenic potential in animals (AFSSA, 2002). Recently Soffritti and colleagues published two reports from studies done on Sprague Dawley rats in which the authors conclude from their data that aspartame is a potential carcinogen (causing brain tumours, lymphomas, leukaemia, transitional cell carcinomas of the renal pelvis and ureter, and malignant schwannomas of peripheral nerves) at normal dietary doses (Soffritti et al., 2005; Soffritti et al., 2006). However after reviewing the data, both the European Food Safety Authority (EFSA) and the FDA discounted the study results because of serious flaws with the study design and conduct (Magnuson et al., 2007).

In 1996, Olney et al. published a report suggesting a link between consumption of aspartame and an increase in the frequency of brain tumours in the United States. The report was an evaluation of data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. The authors note that in the period 1975-1992, there was an increase in the incidence of brain tumours, and the increase was equal in both males and females. Aspartame is proposed to be a promising candidate to explain this rise as it was introduced during the early 1980s; other possible factors were introduced gradually and more recently and most are occupationally linked and hence would not affect males and females in even distribution.

The conclusions of this study have been criticized by many scientists who stated that the methodology, use of data and its interpretation were inappropriate and hence the conclusion invalid. For example, the authors considered the incidence of brain tumours only from 1975 to 1992; when all data is used (1973-1992), it is observed that the incidence of brain tumours started to increase in 1973 and actually stabilised in the mid-1980s (Levy & Hedeker, 1996). Moreover, exposure of the population to aspartame was not measured (it is not known whether the individuals with tumours actually consumed aspartame) and the introduction of magnetic resonance imaging (MRI) in early 1980s could explain the increased detection of tumours (Modan et al., 1992). Similarly, the link between aspartame and breast and prostate cancers

mentioned by Schwartz (1999) was demonstrated to be an ecological fallacy which disregarded other important factors (Trichopoulos, 1999).

Of the 5 other studies investigating the alleged aspartame-cancer link, none recorded an association (Table 2). A case-control study conducted by Gurney et al. (1997) to investigate the link between aspartame and brain cancers, compared 56 cases (US children with brain tumours) to 94 controls. There was no evidence of a casual association between consumption of aspartame and tumours and no indication of a dose response. Similarly, a case-control study conducted in Sweden which included 209 brain tumour cases and 425 controls, found no association between low-calorie drinks and brain tumours (Hardell et al., 2001). Limitations of this study are that it does not report the actual level of consumption of drinks and it did not consider aspartame consumption from other sources (the study was mainly concerned about use of mobile phones).

Another case-control study was conducted in North America to investigate whether maternal diet had any effect on the incidence of medulloblastoma/primitive neuroectodermal tumours (Bunin et al., 2005), the most common brain tumours in children. The cases were 315 mothers of children diagnosed before the age of 6, and the controls were 315 mothers of children not suffering from tumours. After adjustment for confounders, there was no significant association between diet soda intake (both in periconception and midpregnancy) and incidence of medulloblastoma.

The largest relevant human study to date is a prospective one based on the NIH-AARP Diet and Health Study cohort (Lim et al., 2006). 285,079 men and 188,905 women, mean age at entry of 62, were examined for 5 years for the development of brain and hematopoietic cancers. Data was collected at baseline about daily consumption of aspartame from foods, beverages and addition in coffee or tea. The study found was no association between level of aspartame consumption and risk of hematopoietic cancers (RR for  $\geq 600$  mg/day vs. none = 0.98; 95% CI: 0.76-1.27), glioma (RR for  $\geq 400$  mg/day vs. none = 0.73; 95% CI: 0.46-1.15) or their subtypes.

The most recent study investigating the aspartame-cancer link is a case control study conducted in Italy comprising 230 patients and 547 controls (Bosetti et al., 2009). However this study did

not collect data on aspartame in particular but on consumption of sweeteners in general (but aspartame was known to be the main one consumed in the population). No association was found between sweetener consumption and several common neoplasms, with the following Odds Ratios being reported (ever users of sweeteners vs. non users): 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.

**Table 2. Human studies investigating aspartame and cancer risk**

Study	Type and Duration	Population/ Setting	Sample Size and Characteristics	Exposure	Outcome	Comments
Olney et al. (1996)	Epidemiological; 17yrs (1972-1992)	US population	10% of US population from 9 different areas (SEER data)	None measured	Incidence of brain tumours increased in the study period; the authors attribute this increase to the introduction of aspartame	The study did not measure consumption of aspartame, omitted data from 1973 and 1974, and disregarded other factors
Schwartz (1999)	Epidemiological, 35 yrs (1960-1995)	US population	Not reported (data from national surveillance statistics)	None measured	Incidence of breast and prostate cancer increased in the study period; the authors attribute this increase to the introduction of aspartame	The study did not measure consumption of aspartame and disregarded other factors
Gurney et al. (1997)	Prospective case-control; N/A	US children with brain tumours and their mothers vs. healthy controls	56 cases (children with brain tumours), 94 controls matched for sex and age	Data on exposure to dietary factors, including aspartame, in both mothers and children before diagnosis	No association between aspartame consumption and incidence of tumours (several ORs reported, none significant)	Data collected via interviews; ORs adjusted for confounders
Hardell et al. (2001)	Retrospective case-control; N/A	Swedish patients with brain tumours vs. healthy controls	209 cases, 425 controls matched for sex and age	Data on various environmental and dietary factors, including low-calorie drinks	No association between low-calorie drinks and tumours (OR= 1.7, 95% CI= 0.84-3.44)	Data collected via postal questionnaires; did not take into account other sources of aspartame; authors do not report adjusting for confounders
Bunin et al. (2005)	Retrospective case-control; N/A	Mothers of children with medulloblastoma/primitive neuroectodermal tumours diagnosed before the age of 6 vs. mothers with healthy children	315 cases (mothers of children diagnosed before the age of 6), 315 controls (315 mothers of children not suffering from tumours).	Data on pregnancy diet including consumption of diet soda	No association between diet soda and cancer risk (periconception: $\geq 2$ /day vs. none OR=1.3, 95% CI=0.8-2.4; midpregnancy: $\geq 2$ /day vs. none OR=1.3, 95% CI= 0.7-2.5)	Data collected via food frequency questionnaire; did not take into account other sources of aspartame; ORs adjusted for confounders and assessed for various levels of consumption

Lim et al. (2006)	Prospective cohort; 5 yrs	US persons	285,079 men and 188,905 women, aged between 50-71 (mean age 62 at entry)	Data on diet including aspartame-containing foods and beverages and aspartame added to tea or coffee	No association between aspartame consumption and hematopoietic cancers (RR for $\geq 600$ mg/day vs. none = 0.98; 95% CI= 0.76-1.27) or glioma (RR for $\geq 400$ mg/day vs. none = 0.73; 95% CI= 0.46-1.15)	Data collected via food frequency questionnaire; excluded subjects with pre-existing cancers; took into account aspartame consumption from a wide range of food sources; RRs adjusted for confounders
Bosetti et al. (2009)	Retrospective case-control; N/A	Italians with gastric, pancreatic or endometrial cancers vs. healthy controls	230 cases, 547 controls	Data on diet including use of sweeteners	No association between sweetener consumption and cancer risk (ORs for ever users of sweeteners vs. nonusers = 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.	The study was actually an integration of several case-control studies conducted between 1991-2004; data collected was on use of sweeteners in general not aspartame; ORs adjusted for confounders

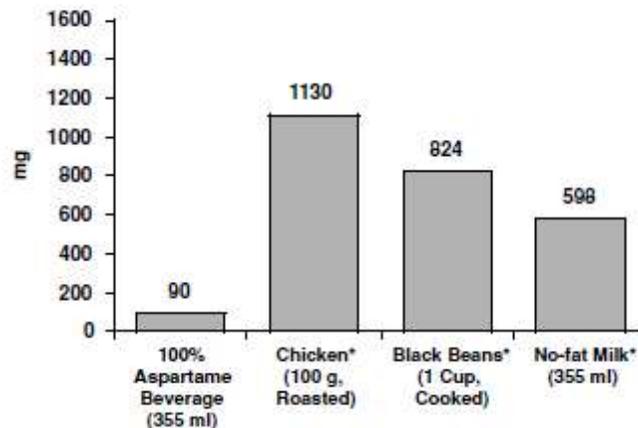
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*OR: odds ratio; RR: relative risk; CI: confidence interval*

## **Behaviour, Mood and Cognitive Function**

Animal studies (in rats and mice) investigating the effects of aspartame on cognitive function, using multiple doses and multiple tests, have documented no effect, even at doses of aspartame up to 4g/kg bw/day, and exposure starting from conception up to 90 days postnatally (Magnuson et al., 2007). The two studies reporting an impairment in learning, one in guinea pig pups (Dow-Edwards et al., 1989) and the other in rats (Christian et al., 2004), both used only one dose (500mg/kg bw/day to pregnant mothers and 250mg/kg bw/day respectively) and one test for learning.

The main component of aspartame is phenylalanine and most studies record an increase in plasma phenylalanine following ingestion of aspartame (EC, 2002); however as seen in figure 3, this is much lower than that occurring after consumption of some common foods.



**Figure 3. Phenylalanine content of a 100% aspartame-sweetened beverage compared to that chicken, black beans and no-fat milk. Source: Stegnik & Filer (1984)**

Phenylalanine is a precursor for tyrosine, dopamine, norepinephrine and epinephrine; a part of plasma phenylalanine also binds to a large neutral amino acid transporter (NAAT) to be carried through the blood brain barrier (Humphries et al., 2008). Phenylalanine competes with tyrosine, tryptophan and methionine for a binding site on the NAAT and hence a large amount of one of these amino acids in the blood will exclude most of the other amino acids from the transporter. A lack of tyrosine and tryptophan in the brain theoretically will result in a drop in dopamine and serotonin respectively. However, randomized controlled human trials to date have found no

indication of behavioural and cognitive dysfunction following aspartame consumption, as described below.

A meta-analysis carried out in 1995 by Walraich et al. investigated whether sugar intake was associated with changes in behaviour or cognition in children (age range: 2-19 years); of the 23 randomized, controlled, double-blinded trials used, 16 used aspartame as the placebo, 4 used a mixture of aspartame and saccharin and 3 used saccharin. Subjects included both normal children and also Attention-Deficit Hyperactivity Disorder (ADHD) patients and children whose parents identified them as 'sugar reactors'. The meta-analysis found that there were no differences in behaviour or cognitive performance between the groups given sugar and those given aspartame/saccharin. A later randomized, controlled, double-blind study carried out by Shaywitz et al. (1994b) involved 15 children with ADHD. These were given either capsules of aspartame (34mg/kg bw/day) or microcrystalline cellulose for a two week period and then crossed over to the other group for another two weeks. Tests of cognition and behaviour found no differences among the groups and there were no changes in urinary levels of neurotransmitters. Plasma phenylalanine levels were higher after 2 hours of aspartame ingestion (from 6  $\mu\text{mol/dl}$  at baseline to 8.5  $\mu\text{mol/dl}$ ). The authors mention that plasma tyrosine levels were also higher following aspartame consumption but do not report the measurements.

Five randomized, controlled, double-blinded trials have been carried out in adults to assess whether aspartame has any effects on behaviour, mood or cognition (Table 3). Ryan-Harshman et al. (1987) challenged 13 healthy males with a large single dose of aspartame (either 5g or 10g) or a placebo in a randomized crossover design. Phenylalanine levels rose from a mean of 7.1 $\mu\text{mol/dl}$  at baseline to 12.6 and 26.4 $\mu\text{mol/dl}$  after 90 minutes of 5g and 10g aspartame ingestion respectively. Tyrosine levels rose slightly but the change was not significant while the tryptophan:other neutral amino acid ratio decreased significantly compared to baseline in both the 5g and 10g aspartame challenge. For both placebo and aspartame groups, there were no changes observed in mood, alertness or food intake. Similarly in a study by Lapierre et al. (1990) 10 healthy volunteers were challenged with a single dose of aspartame (15mg/kg bw) or placebo in a cross-over design. No effects were reported on mood, cognitive function or reaction time.

Following a case report of an adverse reaction allegedly caused by aspartame ingestion in a military pilot, two randomized controlled studies were carried out testing cognitive performance with the SPARTANS test, which has been shown to detect changes in performance of complex aviation-relevant tasks (Table 3). The first study (Stokes et al., 1991) investigated acute aspartame consumption, by giving the subjects (12 healthy pilots) placebo (dextrose) or aspartame (50mg/kg bw/day) or ethyl alcohol (the dose calculated to raise blood alcohol levels by 0.1%; to act as a positive control) with a small carbohydrate meal. Each subject was tested 5 times with each treatment, with a 1 week washout between different treatments. Baseline values were also collected. No difference in cognitive performance was observed in the aspartame and placebo groups, while the ethyl alcohol group exhibited a decline in performance. The second study was aimed to assess the effects of chronic aspartame exposure using the SPARTANS Version 2 test (Stokes et al., 1994). Twelve subjects were given either placebo (dextrose), aspartame (50mg/kg bw/day) or a dose of ethyl alcohol as in the previous study for 9 days with a 7 day washout between each treatment. The test was undertaken on the last day of each treatment. As expected, a significant cognitive decline was observed in the alcohol group. Surprisingly, the aspartame group performed significantly better than the placebo group; the authors attributed this finding to chance.

In a three-way cross-over study, 48 healthy participants were given either sucrose, aspartame at 15mg/kg bw/day or aspartame at 45mg/kg bw/day (Spiers et al., 1998). Treatment periods were 20 days for each, with a 10 day washout between each treatment. Neuropsychologic testing was performed on days 10 and 20 of each treatment while acute effects were assessed on days 10 of each treatment, 1.5 hours after ingestion. No changes in mood or cognitive performance was observed among the groups and the frequency of adverse effects reported (mainly headaches) was the same in all groups. Phenylalanine levels were higher 1.5 hours following ingestion of aspartame, however all other laboratory tests (including measurements for all other amino acids, glucose and insulin) showed no differences among the groups.

**Table 3. Human studies investigating effects of aspartame consumption on behaviour, mood and cognitive function**

Study	Type and Duration	Sample Size and Characteristics	Exposure	Outcome	Comments
Wolraich et al. (1995)	Meta-analysis of 23 RCTs; different durations	Children (560), 'normal', ADHD, and those whom parents identified as 'sugar reactors'	Consumption of sweeteners vs. sugar. Of 23 studies, 16 used aspartame, 4 used mixture of aspartame and saccharin and 3 used saccharin	No difference in behaviour or cognitive performance between groups given sugar or aspartame/saccharin	Includes all RCTs from 1984-1994 investigating behaviour and cognition in children given sugar vs. aspartame/saccharin; pools data from 'normal', ADHD and 'sugar reactors' together
Shaywitz et al. (1994)	RCT, cross-over; 2wks each treatment, 1 wk washout	15 children (11 males, 4 females, 5-13 yrs old) with ADHD	Aspartame (34mg/kg bw/day) vs. placebo (microcrystalline cellulose)	No differences in behaviour or cognitive function; plasma phenylalanine and tyrosine levels higher following aspartame consumption (statistics not reported)	Behavioral and cognitive testing extensive and included the Matching Familiar Figures Test, Children's Checking Task, the Airplane Test, the Wisconsin Card Sorting Test, the Subjects Treatment Emergent Symptom Scale, the Multigrade Inventory for Teachers, and the Conners Behavior Rating Scale
Ryan-Harshman et al. (1987)	RCT, cross-over, single day	13 healthy males (20-35 yrs old)	Single dose of aspartame (either 5g or 10g) or placebo (microcrystalline cellulose)	Aspartame had no effect on mood, alertness or food intake; phenylalanine levels were higher following aspartame consumption (p<0.05)	Mood and alertness tested using the Visual Analogue Scales test describing 17 subjective feelings of hunger, mood and arousal; food intake was monitored
Lapierre et al. (1990)	RCT, cross-over, single day	6 healthy men and 4 healthy women, (21-36 yrs old)	Single dose of aspartame (15mg/kg bw) vs. placebo (microcrystalline cellulose)	Aspartame had no effect on mood, cognitive function or reaction time	Changes in mood measured on visual analog scales, cognitive function determined by digit-symbol substitution test and arithmetic test scores, and reaction time measured with a brake-pedal reaction timer. Memory testing was based on recall of standardized 16-item word lists. Subjects refrained from alcohol, drugs and aspartame for 72 hrs prior to trial
Stokes et al. (1991)	RCT, 3-way cross-over; 1 wk each treatment with 1 wk washout	12 healthy pilots (8 males, 4 females)	Aspartame (50mg/kg bw/day) vs. dextrose vs. ethyl alcohol (dose calculated to raise blood alcohol by 0.1%)	Aspartame had no effect on cognitive performance, while the ethyl alcohol consumption resulted in a decline in cognitive performance	Cognitive performance tested with the SPARTANS test, which has been shown to be sensitive to changes in performance of complex tasks required for aircraft operation

Stokes et al. (1994)	RCT, 3-way crossover; 9 days on each treatment with 1 wk washout	12 healthy college students	Aspartame (50mg/kg bw/day) vs. placebo (dextrose) vs. ethyl alcohol (the dose calculated to raise blood alcohol levels by 0.1%)	Aspartame group performed better in the cognitive test than placebo group; authors attribute this to chance	Cognitive performance tested with SPARTANS Version 2 test
Spiers et al., (1998)	RCT, 3-way cross-over; 20 days on each treatment with 10 days washout	48 healthy subjects (18-34 yrs old)	Sucrose vs. aspartame at 15mg/kg bw/day vs. aspartame at 45mg/kg bw/day	No changes in mood, cognitive performance or adverse effects in group consuming aspartame	Subjects told to avoid alcohol or drugs for 36hrs prior to testing and to avoid consuming aspartame-containing foods throughout the study. Neuropsychologic testing carried out using a computer program that required the subject to compare, copy, and recall alternating trials of verbal and nonverbal stimuli.

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*RCT: randomized controlled trial; hrs: hours; wk: week; yrs: years; ADHD: Attention-Deficit Hyperactivity Disorder*

## **Seizures**

Some animal studies have suggested that aspartame at high doses (up to 4g/kg bw/day) may trigger seizures (Rao et al., 1972); however the vast majority of studies report no association (EC, 2002).

To date, 3 randomized, controlled, double-blinded trials have been carried out to investigate whether aspartame increases the risk of seizures in seizure-prone individuals (Table 4); one study indicated that aspartame might induce seizures while the other two reported no effect. The former involved 10 children recently diagnosed with absence seizures given either aspartame (40mg/kg bw) or sucrose (1g sucrose for every 25mg aspartame) in unsweetened orange juice (Camfield et al., 1992). They were treated once with each substance in random fashion on two consecutive days. The children underwent ambulatory Electroencephalogram (EEG) recording for 1 hour prior to consumption and 6 hours after consumption of the substance. Following aspartame consumption both spike-wave frequency and mean spike-wave length were slightly higher, but not statistically so, compared to sucrose consumption. However, when the total time spent in spike wave per hour of EEG recording was considered, children were found to have significantly higher values following aspartame consumption compared to sucrose (the average number of seconds in spike wave per hour increased by  $40\% \pm 17\%$ ;  $p = 0.028$ ).

On the other hand, in a similar study involving 10 epileptic children given either aspartame (34mg/kg bw/day) or microcrystalline cellulose for two weeks each (cross-over), no effect was observed in measurements of standard 21-lead EEG and continuous 24-hour cassette EEG (Shaywitz et al., 1994a). Unlike the previous study (Camfield et al., 1992), in this study parents were instructed to ensure an aspartame-free diet. EEG readings were taken at the end of each week together with blood samples for hematological and liver function tests and urine samples for creatinine analysis. Plasma phenylalanine and tyrosine levels were higher following aspartame consumption but there were no differences in any of the other parameters. Parents and teachers of the children were also asked to rate the behavior of the children using a modified Conners Behavior Rating Scale; no differences were recorded among the two groups.

Similar results were obtained by Rowan et al. (1995). The authors of this study targeted their recruitment at individuals who had claimed that they suffered seizures after aspartame consumption. In spite of the large number of such claims, only 18 eligible individuals (16 adults and 2 children) were found after 9 years of recruitment. Of these 18 individuals, 14 had recurrent seizures while 4 had only experienced a single seizure. In this randomized, double-blind cross-over study, participants were given either aspartame (50mg/kg bw) or placebo (microcrystalline cellulose) in three divided doses on days 2 and 4, controlling the diets on treatment days. Continuous EEG recording was carried out from days 1 to days 5. While plasma phenylalanine levels were higher following aspartame consumption, no differences in the EEG recordings or sleep patterns were observed in the subjects consuming aspartame compared with those consuming the placebo.

The major limitation of the above three studies is the small number of participants in each (10, 10 and 18). The study which recorded differences in EEG recordings following aspartame consumption (Camfield et al., 1992) was further limited in that diet was not controlled or recorded on treatment days, and it is known that fasting or dehydration can affect seizure susceptibility (Tollefson & Barnard, 1992). In view of the available data, further studies on the effects of aspartame in seizure-susceptible individuals is recommended. Diets during the trials should be controlled or at least ensured that no aspartame-containing foods and beverages are consumed. Until then, seizure-susceptible individuals should use aspartame with caution.

**Table 4. Human studies investigating aspartame consumption and seizure risk**

Study	Type and Duration	Sample Size and Characteristics	Exposure	Outcome	Comments
Camfield et al. (1992)	RCT, cross-over; treated once with each substance on two consecutive days	10 children recently diagnosed with absence seizures	Aspartame (40mg/kg bw) or sucrose (1g sucrose for every 25mg aspartame)	Following aspartame consumption, EEG measurements recorded a longer total time spent in spike wave per hour (increased susceptibility to absence seizures): (average number of seconds in spike wave per hour increased by 40% ± 17%; p = 0.028).	Ambulatory EEG recordings started an hour prior to consumption and continued for 6 hours after consumption; diet was not controlled or recorded; treatment only 1 day
Shaywitz et al. (1994a)	RCT, cross-over, 2 wk on each treatment	10 epileptic children (7 had generalized convulsion with 4 also having absence episodes, 2 had complex partial seizures and 1 had absence seizures)	Aspartame (34mg/kg bw/day) vs placebo (microcrystalline cellulose)	No difference in EEG readings or behaviour	Standard 21-lead EEG and 24 hour cassette EEG readings taken at the end of each week; behaviour assessed by parents and teachers using a modified Conners Behaviour Rating Scale; children were given an aspartame free diet throughout treatment
Rowan et al. (1995)	RCT, cross-over, 5 day trial giving treatments on days 2 and 4	18 individuals (16 adults and 2 children) claiming that they suffered seizures following aspartame consumption (14 had recurrent seizures and 4 only had a single seizure)	Aspartame (50mg/kg bw) vs. placebo (microcrystalline cellulose) in 3 divided doses	No difference in EEG recordings or sleep patterns (p>0.05)	EEG recording was continuous throughout the 5 days; all meals were uniformly standardized on treatment days; treatment only 1 day

*RCT: randomized controlled trial; wk: week*

## **Headaches**

While the internet is replete with reports of aspartame triggering headaches, only 3 clinical trials have been carried out to investigate this link (Table 5). Schiffman et al. (1987) carried out a double blind cross-over trial with 40 individuals who reported getting headaches after ingestion of aspartame. After two days of monitoring, they were given either capsules of aspartame (30mg/kg bw) or placebo on days 3 and 5. There was no difference in the incidence of reported headaches.

Koehler and Glaros (1988) conducted a double-blind cross-over study with 11 subjects who suffered from frequent headaches. The study was over 13 weeks: 4 week baseline, two 4 week treatment periods and 1 week washout between the treatments. Aspartame (300mg) and the placebo were given in capsules. The frequency of headaches reported during the aspartame phase was 3.55, compared to 1.77 and 1.55 during the baseline and placebo phases respectively. Unfortunately the small number of subjects in the study makes it statistically weak.

Similarly, in a double-blind cross-over study with 18 subjects who claimed getting headaches following aspartame consumption, those taking 30mg/kg bw/day for 7 days reported a significantly higher ( $p=0.04$ ) incidence of headaches than those taking the placebo (Van der Eeden et al., 1994). In a different study, 171 patients at the Montefiore Medical Center Headache Unit completed a survey asking whether they believed that alcohol, aspartame or carbohydrates were triggering their headaches (Lipton et al., 1989). 8.2 percent reported aspartame as a precipitating factor (compared to 49.5% indicating alcohol and 2.3% indicating carbohydrates). Having aspartame listed as a possible trigger might have affected the responses, however an interesting fact which emerged was that patients with migraines indicated aspartame as a triggering factor three times more often than those having other types of headaches.

In many of the other aspartame trials carried out in the general population (not headache sufferers) reported in the rest of this review, adverse effects including headaches were recorded and no other study found an association between aspartame and headaches. It thus seems that this link is only present in a small subset of the population (the three studies recording an association

were all carried out in frequent headache sufferers). This must be seen in context of the reported prevalence of headaches associated with other dietary factors, for example citrus fruits (11-22%) cheeses (18-40%) and chocolate (19-33%) (Lipton et al., 1989).

**Table 5. Human studies investigating aspartame consumption and incidence of headaches**

Study	Type and Duration	Sample Size and Characteristics	Exposure	Outcome	Comments
Schiffman et al. (1987)	RCT, cross-over; 5 day trial giving treatments on days 3 and 5	40 individuals who reported getting headaches following aspartame consumption	Aspartame (50mg/kg bw) vs. placebo (microcrystalline cellulose)	No difference in headaches reported (35% in aspartame group, 45% in placebo group; p<0.50)	Controlled diet; single day treatment
Koehler and Glaros (1988)	RCT, cross-over, each treatment given for 4 wks with 1 wk washout	11 subjects who suffered from frequent headaches	Aspartame (300mg, 4 times a day) vs. placebo (microcrystalline cellulose)	Higher incidence of headaches reported during aspartame consumption (mean incidence of headaches during baseline, placebo and aspartame phases: 1.77, 1.55, 3.55 respectively; p<0.02)	Diet was recorded and controlled for
Van der Eeden et al. (1994)	RCT, cross-over; 4 wks alternating treatment each wk	18 subjects claiming that they are sensitive to aspartame	Aspartame (30mg/kg bw/day) vs. placebo (microcrystalline cellulose)	Higher incidence of headaches reported during aspartame consumption (33% of days compared to 24% of days; p=0.04)	Large number of dropouts: from 32 subjects only 18 completed the full protocol; 7 dropped out due to adverse effects
Lipton et al. (1989)	Survey	171 patients at a Headache unit	The survey asked whether they believed that alcohol, aspartame or carbohydrates were causing their headaches	8.2% reported aspartame as a cause (compared to 49.5% indicating alcohol and 2.3% indicating carbohydrates)	Power of suggestion – having aspartame listed as possible trigger; patients with migraines were three times more likely to indicate aspartame as a triggering factor than those having other types of headaches

*RCT: randomized controlled trial; wk: week*

## **Conclusion**

First discovered in 1965, aspartame is now widespread in foods and beverages consumed all over the world. While the main scientific and health authorities are firm in their belief that aspartame is safe, controversies and scares in popular media remain.

Analysis of human studies in this review has shown that consumption is well below the ADI levels, even among high users. The metabolites of this sweetener are compounds found in natural foods and it is a minor source of phenylalanine, aspartic acid and methanol compared to normal dietary intake of other foods. Thus metabolites of aspartame cannot be the source of any adverse effects reported.

There is no evidence that aspartame might be linked to cancer. The epidemiological study by Olney et al. (1996) suggesting that the sweetener was the cause of increasing brain tumours in the United States has been refuted and the higher incidence of tumours recorded has been attributed to, amongst others, the advent of better diagnostic tools (MRI). Four case-control studies in the US, Sweden, North America and Italy found no association between aspartame intake and incidence of cancers; a large five-year prospective cohort study with almost half a million participants also found no association between aspartame use and risk of hematopoietic cancers or glioma (Table 2).

With regards to effects on behaviour, mood and cognitive function, while studies have recorded an increase in plasma phenylalanine levels following aspartame consumption, no changes in behaviour or brain function have been recorded in humans. Studies include a meta-analysis comparing sweeteners to sucrose and 5 randomized controlled trials (Table 3). However, a study in subjects with unipolar depression had to be halted after only 8 subjects had completed the trial due to the severity of reactions within this group (Walton et al., 1993).

Another concern regarding aspartame is whether it is linked to induction of seizures. To date 3 randomized controlled trials in seizure-susceptible individuals have been carried out to investigate this link. One study reported that following a one day treatment with aspartame, EEG

measurements recorded a longer total time spent in spike wave per hour (i.e. aspartame enhances absence seizures) (Camfield et al., 1992). The fact that no indication was provided on whether the children were given any food during the treatment period was a major limitation of this study. On the other hand, the other two studies (one involving a single day treatment (Rowan et al., 1995) and the other using two weeks of treatment (Shaywitz et al., 1994a)) recorded no such effect. Further studies should thus be undertaken to investigate this link.

One of the most common reported side effects from aspartame is headache. To date only 3 human randomized controlled trials have been carried out to investigate this link. The first study, with 40 individuals who reported getting headaches from aspartame, found no difference in the incidence of headaches between aspartame or placebo treatments (Schiffman et al., 1987). On the other hand, a study with 11 subjects who suffered from frequent headaches (Koehler & Glaros, 1988) and another one with 18 subjects who reported being sensitive to aspartame (Van der Eeden et al., 1994), both recorded a significantly higher occurrence of headaches after aspartame consumption. It can thus be concluded that some individuals may be sensitive to aspartame.

In the general population, human studies have indicated that aspartame is safe at and even higher than the ADI. However, a small number of individuals may be particularly sensitive to aspartame and epileptic and persons with a history of depression should use this sweetener with caution. Moreover, aspartame (like other dietary factors including citrus fruits and chocolate) can also be the trigger of headaches in susceptible individuals.

This review discussed only the 'risk' aspect of aspartame use; however one must not forget the benefits associated with the substitution of sugars with the sweetener in foods and beverages. A meta-analysis by De la Hunty et al. (2006) demonstrated that aspartame use was highly correlated with a reduction in energy intake ( $p < 0.0001$ ). Based on data from this meta-analysis it was estimated that daily replacement of one regular carbonated beverage (330ml) with a diet one will result in a 0.1kg weight loss per week (Renwick & Nordmann, 2007). Taking into account that in England, the population has gained an average of 0.007 kg/week over the period 1993-2003, it seems that the use of aspartame has real potential to counteract the average population rate of weight gain (Renwick & Nordmann, 2007).

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