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REVIEW PAPER

A review of the genotoxic and carcinogenic effects of aspartame: does it safe or not?

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Abstract The objective of this article is to review genotoxicologic and carcinogenic profile of the artificial sweetener aspartame. Aspartame is a synthetic dipeptide, nearly 180–200 times sweeter than sucrose. It is the most widely used artificial sweetener especially in carbonated and powdered soft drinks, beverages, drugs and hygiene products. There is a discussion ongoing for many years whether aspartame posses genotoxic and carcinogenic risk for humans. This question led to many studies to specify the adverse effects of aspartame. Therefore, we aimed to review the oldest to latest works published in major indices to gather information within this article. With respect to published data, genotoxicity and carcinogenicity of aspartame is still confusing. So, consumers should be aware of the potential side effects of aspartame before they consume it.

Keywords Aspartame · Genotoxicity · Carcinogenicity · Review

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Introduction

Additives are ingredients which are not usually regarded or used as foods themselves but which are used in or on the food to affect its storage qualities, appearance, taste, texture or to assist in processing steps (Lok et al. 2010). These include preservatives, sweeteners, color additives, flavor enhancers, emulsifiers etc. There are over 3,000 additives approved for use all over the world and artificial sweeteners are one of the important food additives. They have been classified as nutritive and non-nutritive depending on whether they are a source of calories (Whitehouse et al. 2008).

The first recorded sweetener was honey, which was used in the ancient cultures of Greece and China (Bright 1999; Weihrauch and Diehl 2004). Honey was later replaced by saccharose, common sugar, which was originally obtained from sugar cane. The first artificial sweetener was saccharin and it was well accepted during World Wars I and II because of its low production costs and the shortage of regular sugar (Bright 1999; Weihrauch and Diehl 2004). Subsequently cyclamate and aspartame were approved as artificial sweeteners. Saccharin, cyclamate and aspartame, are referred to as 'first generation sweeteners', the others are referred to as 'new generation sweeteners' (Weihrauch and Diehl 2004) such as sucralose, acesulfame K etc.

Food additives are used intensively in factory-made foods, and these must be absolutely safe for human usage. Nevertheless, scientific works report unfavorable results, especially in gene toxicity and carcinogenicity

tests. Genotoxicity pertains to all types of DNA damage (including mutagenicity). Agents that interact with DNA and/or its associated cellular components (e.g. the spindle apparatus) or enzymes (e.g. topoisomerases) are designated genotoxic (Dearfield et al. 2002; Robinson 2010; Jouyban and Parsa 2012). Genotoxicity is sometimes associated with cancer. Especially increased frequency of chromosomal aberrations is linked with different cancer types. Cancer arises from a change in one single cell; the change may be started by external agents and/or inherited genetic factors. It is a leading cause of death worldwide and accounted for 7.6 million deaths (around 13 % of all deaths) in 2008. Deaths from cancer worldwide are projected to continue to rise to over 11 million in 2030 (WHO 2011).

This review is a compendium of the genotoxicity and carcinogenicity data of aspartame that have been reported in the literature up to now. Aspartame is a widely used artificial sweetener among a variety of foods (carbonated and powdered soft drinks, gelatins, chewing gum, yogurt etc.), beverages, drugs and hygiene products (Alleva et al. 2011). The intensive use of aspartame has led researchers to work on its safety. The studies were conducted in laboratory animals and humans, including healthy infants, children, and adults, lactating women, people with diabetes, obese individuals, and people who are carriers of the rare genetic disease phenylketonuria (PKU). Aspartame has been reviewed and determined to be safe by the FDA, the Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organization and the World Health Organization, the Scientific Committee on Food of the European Commission, and the regulatory bodies of over 100 countries (Anonymous 2013a). However; we have found publications that indicate the carcinogenicity and genotoxicity of aspartame. Hence, we decided to provide the information to people, researchers and authorities and in order to open up new frontiers using Pubmed, Scopus, Web of Science, Science-Direct.

Aspartame

Aspartame is a synthetic dipeptide formed by the reaction of L-aspartic acid with L-phenylalanine methyl ester (Rangan and Barceloux 2009). It was discovered by James Schlatter in 1965 and approved as a general purpose sweetener by FDA in 2006. Now aspartame is used in over 5,000 products. It is nearly 180–200 times sweeter than sucrose (Lean and Hankey 2004). FDA has determined the acceptable daily intake (ADI) value of aspartame as 50 mg/kg of body weight/day while the JECFA (Joint FAO/WHO Expert Committee on Food Additives) has set this value as 40 mg/kg of body weight/day (Anonymous 2013b, c). The gastrointestinal tract hydrolyzes aspartame to aspartyl phenylalanine and methanol. Further hydrolysis of aspartyl phenylalanine to aspartic acid and the essential amino acid, phenylalanine, produces a risk for patients with the homozygous gene for PKU (Rangan and Barceloux 2009). Schwartz (1999) argued in his publication that aspartame is partly metabolized to methanol, which itself is converted to formaldehyde, which accumulates within cells and can induce cancer. A recent research conducted in male Wistar rats showed that long term consumption of aspartame leads to an imbalance in the antioxidant/pro-oxidant status in the brain, mainly through the mechanism involving the glutathione-dependent system (Abhilash et al. 2013).

Genotoxicity

Table 1 summarizes publications on the genotoxicity of aspartame. In the Ames assay, aspartame was not found mutagenic at concentrations up to 5,000 μg/plate in the tester strains TA98, TA100, TA1535, TA1537 and TA1538 in both the presence and absence of metabolic activation (Molinary 1978a, b). However, it was found as positive in the Ames assay after nitrosation (Shephard et al. 1993). Molinary (1984) reported that aspartame did not show genetic activity in CD rats using the dominant lethal assay and Purina cesarean rats using host mediated assay. Phenylalanine, a metabolite of aspartame, was found to be mutagenic to *Escherichia coli* K012 uvrB, and it was nonmutagenic in the wild type *E. coli* strains uvrB, uvrB umuC, and uvrB lexA (Sargentini and Smith 1986). Jeffrey and Williams (2000) reported that 1×10^{-2} and 5×10^{-3} M concentrations of aspartame were negative in rat hepatocytes/DNA repair assay in F344 and Sprague–Dawley male rats. Mukhopadhyay et al. (2000) reported that blends of aspartame (3.5, 35, 350 mg/bwkg) and acesulfame-K (1.5, 15 and 150 mg/bwkg) showed no increase in chromosomal aberrations in the bone marrow of Swiss albino mice. Sasaki et al. (2002) have

examined the in vivo genotoxicity of 2,000 mg/kg dose of aspartame for 3 and 24 h in eight mouse organs by comet assay. Authors reported that it did not increase DNA damage in any of the organs studied. Rencüzoğulları et al. (2004) investigated the genotoxic potential of aspartame using chromosome aberration (CA) test, sister chromatid exchange (SCE) test, micronucleus test in human lymphocytes and the Ames/Salmonella/microsome test. They reported that aspartame induced CAs at all concentrations (500, 1,000 and 2,000 μg/ml) and treatment periods (24 and 48 h) dose-dependently, while it did not induce SCEs. On the other hand, aspartame decreased the replication index (RI) only at the highest concentration for the 48 h treatment period. However, aspartame decreased the mitotic index (MI) at all concentrations and treatment periods dose-dependently. In addition, aspartame induced micronuclei at the highest concentrations only. This induction was also dose-dependent for the 48 h treatment period. Aspartame was not mutagenic for *Salmonella typhimurium* TA98 and TA100 strains in the absence and presence of S9 mix. Bandyopadhyay et al. (2008) have studied the genotoxic potential (7–37 mg/bwkg) of aspartame by the comet assay in bone marrow cells of Swiss Albino mice. The authors reported that the comet parameters of DNA were increased in bone marrow cells of Swiss albino mice. Kamath et al. (2010) studied the genotoxic potential of aspartame using micronucleus, chromosomal aberration and sperm morphology tests in animals. 250, 455, 500 and 1,000 mg/kg doses of aspartame were administered in a single dose to four different groups of animals for micronucleus and chromosomal aberration tests. The same doses were administered every day for 1 week for the sperm morphology test. The authors reported that aspartame at doses of 455, 500 and 1,000 mg/kg showed a significant ($P < 0.01$) increase in the number of micronucleated polychromatic erythrocytes, total aberrations and abnormal sperms. The authors have concluded that aspartame is a clastogenic agent. Alsuhaibani (2010) reported that 3.5, 35, 350 mg/kg body weight doses of aspartame induced dose dependently chromosome aberrations while it did not induce sister chromatid exchanges in bone marrow cells of Swiss albino mice. On the other hand, aspartame did not decrease the mitotic index (MI). In another study, aspartame was administered orally to pregnant rats and cytogenetic effects were observed in mother rats and their offsprings (Abd Elfatah et al. 2012). The authors have reported that aspartame increased chromosomal aberrations and DNA fragmentation in the liver and bone marrow of mother albino rats and their offsprings. Kashanian et al. (2013) examined the interaction of aspartame with DNA using spectrophotometric, spectrofluorometric competition experiment and circular dichorism techniques. The authors suggested that aspartame interacts with calf thymus DNA via groove binding mode with an intrinsic binding constant of 5×10^{-4} M.

Carcinogenicity

Animal studies

The role of sweeteners in cancer risk has been widely debated since the 1970s, when animal studies found an excess risk of bladder cancer in rodents treated with extremely high doses of saccharin (Weihrauch and Diehl 2004; Bosetti et al. 2009). Animal studies showed that aspartame has not any cancer-inducing effects in 860 SCL Wistar rats (Ishii 1981) and in male F344 rats (Hagiwara et al. 1984). However, Olney et al. (1996) and Schwartz (1999) reported that aspartame and its metabolites, phenylalanine and methanol, increased the different cancer types including, brain, prostate and breast cancers in rats. Aspartame increased the incidence of malignant tumor in Sprague–Dawley rats, with a significant positive trend in both sexes, and in particular in females treated at 50,000 ppm ($P \leq 0.01$) when compared to controls. An increase in lymphomas–leukemias was observed in both sexes, and in particular in females 400, 2,000, 10,000, 50,000, 100,000 ppm caused an increase in lymphomas–leukemias. A statistically significant increase of transitional cell carcinomas of the renal pelvis and ureter were determined in females particularly at 100,000 ppm. An increased incidence of malignant schwannomas of the peripheral nerves was observed in males (Soffritti et al. 2006). The results of this mega-experiment indicate that aspartame, in the tested experimental conditions, is a multi-potential carcinogenic agent (Table 2).

Epidemiological studies

There are some remarkable contradictory results found in the epidemiological studies. Olney et al. (1996) reported the relationship between increasing frequency of brain tumors in humans since 1980 and the use of

Table 1 Reports on the genotoxicity of the aspartame

Test material	Genotoxic end-point	Results	References
S. typhimurium TA98, TA100, TA153, TA1538	Frame-shift mutation/base pair substitution	−	Molinary (1978a, b)
AMES	Frame-shift mutation/base pair substitution	+	Shephard et al. (1993)
CD rats	Dominat lethal assay	−	Molinary (1984)
Purina cesarean rats	Host mediated assay	−	Molinary (1984)
E. coli uvrB, uvrB umuC and uvrB lexA	Mutagenicity (phenylalanine, a metabolite of aspartame)	−	Sargentini and Smith (1986)
E. coli K012 uvrB	Mutagenicity (phenylalanine, a metabolite of aspartame)	+	Sargentini and Smith (1986)
F344, Sprague–Dawley male rats	Rat hepatocytes/DNA repair assay	−	Jeffrey and Williams (2000)
Swiss albino mice/bone marrow	Chromosomal aberration	−	Mukhopadhyay et al. (2000)
Mouse organs	Comet assay	−	Sasaki et al. (2002)
Human lymphocytes	Chromosomal aberrations	+	Rencüzoğulları et al. (2004)
Human lymphocytes	Sister chromatid exchanges	−	Rencüzoğulları et al. (2004)
Human lymphocytes	Micronuclei	+ (2,000 μg/ml)	Rencüzoğulları et al. (2004)
Human lymphocytes/cytotoxicity	Replication index	+ (2,000 μg/ml-48 h)	Rencüzoğulları et al. (2004)
Human lymphocytes/cytotoxicity	Mitotic index	+	Rencüzoğulları et al. (2004)
S. typhimurium TA98, TA100	Frame-shift mutation/base pair substitution	−	Rencüzoğulları et al. (2004)
Swiss albino mice/bone marrow	Comet assay	+	Bandyopadhyay et al. (2008)
Swiss albino mice/bone marrow and peripheral blood	Micronucleus	+	Kamath et al. (2010)
Swiss albino mice/bone marrow	Chromosomal aberration	+	Kamath et al. (2010)
Swiss albino mice	Sperm morphology	+	Kamath et al. (2010)
Swiss albino mice/bone marrow	Chromosomal aberrations	+	Alsuhaibani (2010)
Swiss albino mice/bone marrow	Sister chromatid exchanges	−	Alsuhaibani (2010)
Swiss albino mice/bone marrow	Mitotic index	−	Alsuhaibani (2010)
Albino rats and their offspring	Chromosomal aberrations and DNA fragmentation	+	Abd Elfatah et al. (2012)
Calf thymus DNA	DNA binding	+	Kashanian et al. (2013)

+ Positive, − negative

aspartame. A case–control study on aspartame consumption was conducted in children with brain tumors. 56 patients and 94 controls were compared in terms of aspartame use. They observed no elevated brain tumor risk for the child from maternal consumption of aspartame during pregnancy (Gurney et al. 1997). Artificial sweeteners and the risk of pancreatic cancers have been studied by the Schernhammer et al. (2005) among 88,794 women and 49,364 men without cancer at baseline; they documented 379 cases of pancreatic cancer during up to 20 years of follow-up. The authors have reported that soft drink consumption did not influence pancreatic cancer risk among men; however in women consumption of sugar-sweetened soft drinks may be associated with a modest risk. Lim et al. (2006) examined 285,079 men and 188,905 women ages 50–71 years who consumed four aspartame-containing beverages (soda, fruit drinks, sweetened iced tea, and aspartame added to hot coffee and tea). During over 5 years of follow-up (1995–2000), 1,888 hematopoietic

Table 2 Carcinogenicity of the aspartame in animal models

Test material	Carcinogenicity model	Results	References
860 SCL Wistar rats	Brain tumor	−	Ishii (1981)
Male F344 rats	Brain and bladder tumors	−	Hagiwara et al. (1984)
Rat	Brain, prostate and breast tumors	+	Olney et al. (1996) and Schwartz (1999)
Sprague–Dawley male and female rats	Lymphoma, leukemia	+	Soffritti et al. (2006)
Sprague–Dawley female rats	Transitional cell carcinoma of the renal pelvis and ureter	+	Soffritti et al. (2006)
Sprague–Dawley male rats	Malignant schwannomas of peripheral nerve	+	Soffritti et al. (2006)

+ Positive, − negative

cancers and 315 malignant gliomas were ascertained. They have concluded that there was no relation with aspartame consumption and risk of overall hematopoietic cancer and glioma or their subtypes in men and women. Andreatta et al. (2008) compared 197 patients with histologically confirmed urinary tract tumors with 397 controls between 1999 and 2006 in Argentina. The authors reported that the risk of urinary tract tumors was significantly increased in long-term (≥10 years) exposure to artificial sweeteners, including aspartame. In a study on cancer risk associated with the consumption of artificial sweeteners done in Italy between 1994 and 2001, Bosetti et al. (2009) analysed 230 patients with tumor incidence, histologically confirmed cancers of the stomach with 547 corresponding controls, 326 with cancer of the pancreas with 652 controls, and 454 with cancer of the endometrium with 908 controls. Schernhammer et al. (2012) assessed diet in the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS). The authors identified 1,324 non-Hodgkin lymphomas (NHLs), 285 multiple myelomas, and 339 leukemias patients. Their findings showed that there was no significant association between soda intake and risks of NHL and multiple myeloma in women. However, in men, ≥1 daily serving of diet soda increased risks of NHL and multiple myeloma (Table 3).

Discussion and conclusions

Table 1 summarizes the genotoxicity profile of aspartame. A total of 24 assessments were reported in 15 articles and chromosomal aberrations tests were most often used. The percentage of positive results was nearly 55 %. Considering all the data we can state that aspartame is a moderate genotoxic agent. The quantitative data on aspartame carcinogenicity in animal models are summarized in Table 2. A total of 11 assessments were reported in five articles. Among them the percentage of the positive results was 73 %. Brain, prostate, breast tumors, lymphoma, leukemia, cell carcinoma of the renal pelvis and ureter, malignant schwannomas of peripheral nerves were observed in rats. Higher proportion of the positive results indicates that aspartame is most probably a carcinogenic additive to animals. In addition, in epidemiological studies the percentage of the positive results was lower than in animal models. Nearly 45 % of the existing results yielded as positive. Brain tumor, NHL, leukemia, urinary tract tumors and multiple myeloma were reported in three articles. Therefore, long-term exposure can play an important role in the development of aspartame induced cancer which is stated in the reviewed literature. We know that human bio-monitoring studies for food additives are not possible since large numbers of reasons can be responsible for the tumorogenesis, for example life style, nutritional status, stress, smoking, alcohol use, occupational exposure etc. Therefore, in vivo and in vitro tests become more important methods than epidemiological studies to test potential genotoxicity and carcinogenicity of food additives. So, consumers should be aware of the side effects of aspartame before they consume. Further genotoxicity and carcinogenicity studies should be conducted to reach a clear view on its safety.

Table 3 Carcinogenicity of the aspartame in epidemiological studies

Study design	Carcinogenicity model	Results	References
Human	Brain tumor	+	Olney et al. (1996)
Children (56 patients and 94 controls)	Brain tumor	−	Gurney et al. (1997)
88,794 Women and 49,364 men (379 cases)	Pancreatic cancer	−	Schernhammer et al. (2005)
285,079 Men and 188,905 women (1,888 hematopoietic cancers and 315 malignant gliomas)	Hematopoietic cancer and malignant glioma	−	Lim et al. (2006)
197 Patients and 397 controls	Urinary tract tumors	+	Andreatta et al. (2008)
230 Patients and 547 controls (stomach), 326 patients and 652 controls (pancreas), 454 patients and 908 controls (endometrium)	Stomach, pancreas and endometrium cancers	−	Bosetti et al. (2009)
1,324 Non-Hodgkin lymphomas (NHLs), 285 multiple myelomas, and 339 leukemias	Non-Hodgkin lymphomas, multiple myelomas, leukemias	− (Woman) + (Men)	Schernhammer et al. (2012)

+ Positive, − negative

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