Aspartame: Basic Information for Toxicologists

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Abstract

Background: Aspartame is one of the most widely used artificial sweeteners in over 90 countries worldwide in over 6000 products, including carbonated and powdered soft drinks, hot chocolate, chewing gum, candy, desserts, yogurt, and tabletop sweeteners, as well as some pharmaceutical products like vitamins and sugar-free cough drops. Aspartame has been shown to induce oxidative stress and lipid peroxidation; most serious effects result from chronic exposure due to these effects. Also it shows organ and species toxicity with relation to the liver, kidney, brain, testis and other organs. **The aim of this study** is to spotlight on aspartame, the most widely used artificial sweetener regarding benefits and Hazards. This essay was conducted by reviewing the literature, researches, and textbooks dealing with aspartame. Conclusion: We found that aspartame is a good& **beneficial** artificial sweetener; FDA approved a safe daily dosage of 40 mg/kg/ day regarding diabetes and obesity. **Harmful** if used in larger doses regarding neurobehavioral, hepatic, testicular and other organ dysfunction, however it has no effects on breastfeeding or carcinogenic effects**.Therfore, the role** of physicians is to adjust the dose of aspartame to that which approved by FDA and do more clinical studies to detect more benefits and hazards.

Introduction

Aspartame is an artificial non-saccharide sweetener used as a sugar substitute in some foods and beverages (**Budavari, 1989**). It was first sold under the brand name NutraSweet. It was first made in 1965, and the patent expired in 1992. It was initially approved for use in food products by the U.S. Food and Drug Administration (FDA) in 1981. The safety of aspartame has been the subject of several political and medical controversies, United States congressional hearings, and Internet hoaxes **(Mikkelson, 2015).**

Chemistry

Aspartame is a methyl ester of the dipeptide of the natural amino acids L-aspartic acid and L-phenylalanine. Under strongly acidic or alkaline conditions, aspartame may generate methanol by hydrolysis. Under more severe conditions, the peptide bonds are also hydrolyzed, resulting in free amino acids. Figure (1) **(Ager et al., 1998)**

Metabolites

Aspartame is rapidly hydrolyzed in the small intestines. Even with the ingestion of very high doses of aspartame (over 200 mg/kg), no aspartame is found in the blood due to the rapid breakdown **(Magnuson et al 2007)**. Upon ingestion, aspartame breaks down into residual components, including aspartic acid, phenylalanine, methanol,(Roberts et al, 2004) in ratio of 4:5:1 by mass**(Humphries et al., 2008)**and further breakdown products including formaldehyde and formic acid. Human studies show that formic acid is excreted faster than it is formed after ingestion of aspartame. In some

amount produced from aspartame in beverages. **(Stegink, 1987)** fruit juices, higher concentrations of methanol can be found than the

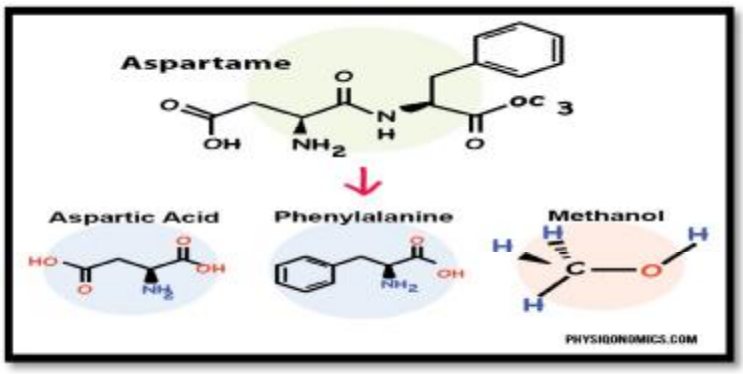

Fig (1) Chemical structure and metabolites of aspartame (Budavari, 1989)

Intake:

The acceptable daily intake (ADI) value for aspartame, as well as other food additives studied, is defined as the "amount of a food additive, expressed on a bodyweight basis that can be ingested daily over a lifetime without appreciable health risk."(WHO, 1987) The Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Commission's Scientific Committee on Food have determined this value is 40 mg/kg of body weight for aspartame, while FDA has set its ADI for aspartame at 50 mg/kg **(Renwick, 2006).**

Commercial uses:

Aspartame is an ingredient in approximately 6,000 consumer foods and beverages sold worldwide, including (but not limited to) diet sodas and other soft drinks, instant breakfasts, breath mints, cereals, sugar-free chewing gum, cocoa mixes, frozen desserts, gelatin desserts, juices, laxatives, chewable vitamin supplements, milk drinks, pharmaceutical drugs and supplements, shake mixes, tabletop sweeteners, teas, instant coffees, topping mixes, wine coolers and yogurt. It is provided as a table condiment in some countries.

Aspartame is less suitable for baking than other sweeteners, because it breaks down when heated and loses much of its sweetness **(Choudhary and Pretorius, 2017).**

Mechanism of action:

The gustatory system recognizes chemical stimuli that elicit 1 of 5 distinct perceptual qualities: sweet, sour, salty, bitter, and umami (the savory taste of glutamate).Stimulus detection occurs through specialized taste cells, clustered together in small groups (taste buds) found predominantly on the dorsal surface of the tongue and soft palate. Activation of these cells by taste stimuli releases neurotransmitters onto afferent cranial nerve fibers, causing transmission of taste information to the brain. The brain then processes this taste information, along with other sensory information (including olfactory, thermal and textural), to elicit the perception of flavor and in the context of experience, motivation, preference and hedonic valence to promote an appropriate ingestive response **(John et al., 2012).**

Uses: Aspartame is approximately 200 times sweeter than sucrose. Due to this property, even though aspartame produces four

kilocalories of energy per gram (17 kJ/g) when metabolized, the quantity of aspartame needed to produce a sweet taste is so small that it's caloric contribution is negligible. **(Magnuson et al., 2007 and O' Donnelle, 2006).**

Health Effects:

Aspartame has been deemed safe for human consumption by over 100 regulatory agencies in their respective including the UK Food (countries, Standards Agency, the European Food Safety Authority (EFSA) and Health Canada **(Butchko et al, 2002)**.

Breastfeeding:

In a study done in 1979, the effect of aspartame ingestion on blood and milk amino acid levels in lactating women was tested. A previous study resulted in the conclusion that aspartame administration at 50 mg/kg body weight has a small effect upon the milk aspartate levels; and, although a small increase in aspartate time-effect scores was noted over the four-hour post-absorptive period, no significant difference was noted over the entire 24-hour watching period **(Stgink et al., 1979)**.

Cancer:

Reviews have found no association between aspartame and cancer. These reviews have looked at numerous carcinogenicity studies in animals, epidemiologic studies in humans, as well as in vitro genotoxicity studies. These studies have found no significant evidence that aspartame causes cancer in animals, damages the genome, or causes cancer in humans at doses currently used **(Marinovich et al., 2013 and Kirkland & Gatehouse, 2015**).

Neurological and psychiatric symptoms: Numerous allegations have been made via the Internet and in consumer, magazines purporting neurotoxic effects of aspartame leading to neurological or psychiatric symptoms such as seizures, headaches, and mood changes. **(EFSA national, 2010)**

Headaches: Headache is a common symptom reported by consumers.While one small review noted aspartame is likely one of many dietary triggers of migraines, in a list that includes "cheese, chocolate, citrus fruits, hot dogs, monosodium glutamate, aspartame, fatty foods, ice cream, caffeine withdrawal, and alcoholic drinks, especially red wine and beer**," (Millichap and yee, 2003)**. Other reviews have noted conflicting studies about headaches. **(Magnuson et al., 2007 and Sun-Edelstein & Mauskop, 2009)**.

Toxicity to the liver: The current issues provided evidence that aspartame increases oxidative stress in the liver. Increase the serum AST, ALT and GGT activities as well as a remarkable elevation in the concentration serum total cholesterol, triglycerides, and LDL. These data are sensitive indicators of liver injury **(Ozer, 2008; Egbuonu, 2009 & Abhilash et al., 2011)** Also, many issues showed that the major target organ in ASP poisoning is liver and the primary lesion is acute centrilobular hepatic necrosis. **(Ashok and Rathinasamy, 2014 and Alipour, 2013)** ASP is metabolized in the gastrointestinal tract into aspartic acid, phenylalanine, and methanol. However, aspartic acid is mostly eliminated through the lungs in the form of carbon dioxide. Also some of the phenylalanine formed in the intestine following ingestion of ASP is excreted in the form of CO2 most of it is incorporated into the pool of amino acids and contributes to protein synthesis. Moreover, methanol is primarily metabolized by oxidation to formaldehyde and then to format. These processes are accompanied by the formation of superoxide anion and hydrogen peroxides, Protein and

albumin depletion results in increased toxicity to ASP, which is associated with a significantly decreased rate of hepatic metabolism **(Abhilash et al., 2011 and Darwish et al 2015**

Effects on the testes: Aspartame damages the hypothalamus. The hypothalamus produces gonadotropin-releasing hormone (GRH). The GRH goes down the stalk between the hypothalamus and pituitary and causes the pituitary then to produce gonadotropins. The ganglion goes to the testicles and causes them to produce testosterone without which there is no sexual drive or pleasure for either. In the original studies aspartame triggered atrophied testes and testicular tumors **(James, 2000 and Puica et al., 2009).**

Summary and Conclusion:

Aspartame is one of the most widely used artificial sweeteners in over 90 countries worldwide in over 6000 products, including carbonated and powdered soft drinks, hot chocolate, chewing gum, candy, desserts, yogurt, and tabletop sweeteners. Aspartame has been shown to induce oxidative stress and lipid peroxidation; most serious effects result from chronic exposure due to these effects. Also, it shows organ and species toxicity with relation to the liver, kidney, brain, testis and other organs.

Recommendations:

- Diet of people consuming aspartame should be less than the FDA approved dose of 40 mg/kg.bw .day .however it remains questionable.
- Chronic aspartame intake causes liver and testicular damage at both biochemical and histopathological levels.
- Further studies should be carried out on chronic aspartame toxicity and its effects on liver enzymes other than AST, ALT like GGT, AFP….etc.

References

1- Abhilash, M.; Paul, M.V.; Varghese, M.V.; Nair, R.H. (2011): Effect of long term intake of aspartame on antioxidant defense status in liver, Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc., 49:1203–1207.

2-Ager, D.J.; Pantaleone , D.P.; Henderson, S.A.; Katritzky, A.R.; Prakash, I.; Walters, D.E. (1998): "Commercial, Synthetic Non-nutritive Sweeteners". Angewandte Chemie International Edition, 37: (13–24): 1 **Alipour, M.C. (2013):** Therapeutic effect of liposomal-N-acetylcysteine against acetaminophen-induced hepatotoxicity. J Drug Target, Early Online. 1–8. 802–1817.

3-Ashok, D.W.; Rathinasamy, S.W.(2014): Long-term effect of aspartame on the liver antioxidant status and histopathology in Wistar albino rats. Biomedicine & Preventive Nutrition. 4 (2): 299–05.

4-Budavari, S. (1989): Aspartame. The Merck Index (11th ed.). Rahway, NJ: Merck & Co. p. 859-861.

5-Butchko, H.H.; Stargel , W.W.; Comer, C.P.; Mayhew, D.A.; Benninger, C.and Blackburn, G.L.(2002) : Aspartame: review of safety. Regulatory Toxicology and Pharmacology. 35 (2 Pt 2): S1–93.

6-Choudhary, A.K. and Pretorius, E. (2017): Revisiting the safety of aspartame". Nutrition reviews. 75 (9): 718–730.

7-Darwish, A.; Eman, S.h. M.G. and El-Said (2015): Effect of N-acetylcysteine (NAC) On Hepatotoxicity of Aspartame. Egypt. J. Chem. Environ. Health, 1 (1):389-399.

8-EFSA National Experts (May 2010): Report of the meetings on aspartame with national experts. EFSA.

9-Egbuonu, A. C. (2009): Hepatotoxic effects of low dose oral administration of monosodium glutamate in male albino rats. African Journal of Biotechnology .8 (13) 303-35.

10-Humphries, P.; Pretorius, E. and Naudé , H. (2008): Direct and indirect cellular effects of aspartame on the brain. European Journal of Clinical Nutrition. 62 (4): 451–62.

11-James, B. (2000): Mal sexual dysfunction triggered by aspartame. The spectrum (1), 11.p 8.

12-John, D.; Fernstrom; Steven, D.; Munger; Anthony, S.; Ivan, E.; Araujo, D.; Ashley, R. and Samuel, M. (2012): Mechanisms for SweetnessJ Nutr. 142(6): 113–114.

13-Kirkland, D. and Gatehouse, D. (2015): Aspartame: A review of genotoxicity data. Food and Chemical Toxicology. 84: 161–8.

14-Magnuson, B.A . ; Burdock , G.A . ; Doull , J . ; Kroes , R.M . ; Marsh , G . M.; Pariza, M.W.; Spencer, P.S.; Waddell, W.J.; Walker, R. and Williams G.M. (2007): Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. Crit. Rev. Toxicol., 37(8): 629-727.

15-Marinovich, M.; Galli, C.L.; Bosetti, C.; Gallus, S.and La Vecchia, C. (2013): Aspartame, low-calorie sweeteners, and disease: regulatory safety and epidemiological issues. Food and Chemical Toxicology. 60: 109–15.

16-Michelson, D. (2015): FALSE: Aspartame — Sweet Poison". Snopes. Retrieved 3 May 2017.

17-Millichap, J.G. and Yee, M.M. (2003): The diet factor in pediatric and adolescent migraine. Pediatric Neurology. 28 (1): 9–15.

18- O'Donnell, K. (2006): Aspartame and Neotame. In Mitchell HL. Sweeteners and sugar alternatives in food technology. Blackwell. pp. 86–95.

19-Ozer, J. (2008): The current state of serum biomarkers of hepatotoxicity. Toxicology. 20; 245(3):194-05.

20-Puica, C . ; Craciun, C.; Rusu, M.; Cristescu, M . ; Borsa, M . and Roman, I. (2009): Ultrastructural aspects concerning the hypothalamus-pituitary complex reactivity following chronic administration of aspartame in juvenile rats. Studia Universitatis "Vasile Goldiş" Seria Ştiinţele Vieţii, 19(1), 19-24.

21-Renwick, A.G. (2006): The intake of intense sweeteners - an updated review. Food Additives and Contaminants. 23 (4): 327–38.

22-Stegink, L .D. (1987): The aspartame story: a model for the clinical testing of a food additive. The American Journal of Clinical Nutrition. 46 (1 Suppl): 204–15.

23-Stegink, L. D . ; Filer, L.J., and Baker, G.L. (1979): Plasma, erythrocyte and human milk levels of free amino acids in lactating women administered aspartame or lactose. The Journal of Nutrition. 109 (12): 2173–81.

24-Sun-Edelstein, C. and Mauskop, A . (2009): Foods and supplements in the management of migraine headaches. The Clinical Journal of Pain. 25 (5): 446–52.