Artificial Sweeteners
Sourab Gupta*, Vivek Mahajan, Shagun Mahajan**, Vishal R. Tandon

Introduction
In recent years there has been a steady and significant increase in consumer demand for low calorie products in the forms of food & drinks. As a result there is growing interest among healthcare professionals and the general public to learn more about low calorie sweeteners.

Artificial sweeteners / low calorie sweeteners are synthetic sugar substitutes but may be derived from naturally occurring substances, including herbs or sugar itself (1). Artificial sweeteners are also known as intense sweeteners because they are many times sweeter than regular sugar. Artificial sweeteners currently approved by the Food and Drug Administration (FDA) are (1,2):

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<th>Table 1</th>
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Possible Health Benefits of Artificial Sweeteners

**Weight Control**
One of the most appealing aspects of artificial sweeteners is that they are non-caloric. Although they are not a 'silver bullet', low calorie sweeteners can help people reduce their calorie intakes. Long-term trials consistently indicate that the use of low calorie sweeteners results in slightly lower energy intakes and that if low calorie sweeteners are used as substitutes for higher energy-yielding sweeteners, they have the potential to aid in weight management (3,4).

**Diabetes**
People with diabetes have difficulty in regulating their blood sugar levels. Low calorie sweeteners offer people with diabetes broader food choices by providing the pleasure of the sweet taste without raising blood glucose. As low calorie sweeteners have no impact on insulin and blood sugar levels and do not provide calories, they can also have a role in weight loss and weight control for people with type II diabetes (5,6).

**Dental Cavities**
When sugar-sweetened foods and drinks are consumed, the bacteria present in the mouth converts the sugar to acid. If this acid is not removed by teeth cleaning, it can wear away the surface enamel, eventually causing cavities to form. Low calorie sweeteners are not fermentable and do not contribute to tooth decay. By improving palatability, low calorie sweeteners can also encourage the use of toothpastes, mouthwashes and fluoride supplements that assist dental hygiene (7).

Possible Health Concerns of Artificial Sweeteners

**Cancer**
Since their introduction, the role of artificial sweeteners on cancer risk has been widely debated. They have been the subject of intense scrutiny for decades. That's largely because of studies dating to the 1970s that linked saccharin to bladder cancer in laboratory rats, later was shown that the carcinogenic effect of saccharin is species specific.

In 2006 the Cesare Maltoni Cancer Research Center of the European Ramazzini Foundation conducted a long-term bioassay on aspartame (APM), a widely used artificial sweetener & results of this mega-experiment indicated that APM is a multipotential carcinogenic agent, even at a daily dose of 20 mg/kg body weight, much less than the current acceptable daily intake (8).

A case-control study of 480 men and 152 women in Canada found a positive association between the use of artificial sweeteners, particularly saccharin, and risk of bladder cancer. The risk ratio for ever versus never used is 1·6 for males and a significant dose-response relationship was obtained for both duration and frequency of use. This fuelled the controversy and led to ban of saccharin in Canada (9). Andreatta MM et al (10) in a case-control study found that regular use of AS for 10 years or more was positively associated with Urinary Tract Tumors.

Although there are some animal studies and few epidemiologic studies also found some associations between artificial sweeteners and cancer risk in humans, but most human studies fail to support this association.

Weihrauch and Diehl in their review divided artificial sweeteners in 'first generation' sweeteners such as saccharin, cyclamate and aspartame, and found there is no evidence to suggest their carcinogenic risk but for

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Although artificial sweeteners became popular for they can help reduce weight but epidemiologic data suggest an association between artificial sweetener use and weight gain. A prospective cohort study on drinkers of artificially sweetened beverages consistently had higher BMIs at the follow-up, with dose dependence on the amount of consumption. Average BMI gain was +1.01 kg/m² for control and 1.78 kg/m² for people in the third quartile for artificially sweetened beverage consumption (15). Similar observations have been reported in children, wherein a two-year diet soda consumption was associated with higher BMI Z-scores indicating weight gain (16). Intervention studies suggest that artificial sweeteners do not help reduce weight when used alone. Their addition to diets poses no benefit for weight loss or reduced weight gain without energy restriction and exercise (4,17). There are concerns that inclusion of artificial sweeteners in the diet causes overcompensation for the expected caloric reduction thereby promoting energy intake and contributes to obesity.

Nettleton JA et al (18) determined associations between diet soda consumption and risk of incident metabolic syndrome, its components, and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis and found consumption of diet soda at least daily was associated with significantly greater risks of select incident metabolic syndrome components and type 2 diabetes (18).

While de Koning L et al (19) in their cohort study found the association between artificially sweetened beverages and type 2 diabetes.

Preload experiments generally have found that sweet taste, whether delivered by sugar or artificial sweeteners, enhanced human appetite and thereby subsequent increase energy intake (20).

**Migraine**

In other published reports, Blumenthal (1997) reported three case studies wherein experienced migraines while chewing a popular gum with aspartame additive. In all cases, the migraines were relieved after cessation of product use. The headaches were reproducible by reintroducing the gum (21). Bigal & Krymchantowski (2006) also reported migraine to get triggered by sucralose (22).

### Table 1. List of FDA approved Artificial Sweeteners

<table>
<thead>
<tr>
<th>Artificial Sweetener</th>
<th>Composition</th>
<th>Caloric Value</th>
<th>Acceptable Daily Intake ADI</th>
<th>Uses</th>
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<tbody>
<tr>
<td>Acesulfame Potassium</td>
<td>A combination of an organic acid and potassium</td>
<td>4 kcal/g</td>
<td>Up to 500 times</td>
<td>in drinks, foods, tabletop sweeteners, oral-care and pharmaceutical products</td>
</tr>
<tr>
<td>Aspartame</td>
<td>Two amino acids: aspartic acid and phenylalanine.</td>
<td>Calorie free</td>
<td>0-15 mg/kg</td>
<td>Used as a tabletop sweetener in drinks, chewing gums, salad dressings and jams</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>Cyclamic acid, sodium or calcium salt</td>
<td>Calorie free</td>
<td>0-2 mg/kg</td>
<td>Used as a tabletop sweetener in drinks, desserts, confectionery and also in pharmaceutical products</td>
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<tr>
<td>Neotame</td>
<td>Derivative of aspartame</td>
<td>Calorie free</td>
<td>0-5 mg/kg</td>
<td>Used in baked goods, desserts, ice-cream and dairy products, breakfast cereals and confectionery</td>
</tr>
<tr>
<td>Saccharin</td>
<td>Sodium or calcium saccharate</td>
<td>Calorie free</td>
<td>Up to 500</td>
<td>Used in bakery products, desserts, ice-cream and dairy products, breakfast cereals and confectionery</td>
</tr>
<tr>
<td>Sucralose</td>
<td>Derived from sugar</td>
<td>Calorie free</td>
<td>Up to 600</td>
<td>Used in baked goods, desserts, ice-cream and dairy products, breakfast cereals and confectionery</td>
</tr>
</tbody>
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*new generation' sweeteners such as acesulfame-K, sucralose and neotame it is too early to establish any epidemiological evidence about possible carcinogenic risks. However, according to the current literature, the possible risk of artificial sweeteners to induce cancer seems to be negligible (11). Gallus et al 2007 (12) reviewed several case-control studies and found a lack of association between saccharine, aspartame, and other sweeteners and several common neoplasms. Magnuson BA review aspartame safety based on current use levels, regulations, and toxicological and epidemiological studies and found no evidence to support an association between aspartame and cancer in any tissue (13). Bosetti et al (14) added further evidence on the absence of an adverse effect of low-calorie sweetener (including aspartame) consumption on the risk of Gastric, Pancreatic, and Endometrial Cancers (14).
Preterm Delivery
A prospective cohort analyses of 59,334 women from the Danish National Birth Cohort (1996-2002) concluded that daily intake of artificially sweetened soft drinks may increase the risk of preterm delivery (23).

Hepatotoxicity
A case study of the hepatotoxicity of saccharin was published in 1994. A patient presented with elevated serum concentrations of liver enzymes after the oral administration of three different drugs, of which saccharin was the only common constituent (24).

Thrombocytopenia
Additionally, a case report in 2007 revealed four individuals with thrombocytopenia attributed to products containing aspartame (25).

Conclusion
Although artificial sweeteners have gained attention as dietary tools to help curtail the obesity epidemic, enhancing flavour while reducing calories, and assist in weight-loss. But key question is their safety; especially in susceptible populations for the potential deleterious effects of artificial sweeteners include diabetics, children, pregnant women, breastfeeding mothers, individuals with low seizure thresholds, and individuals at risk for migraines. More studies are required for these susceptible populations. Because of their presence in more than 6,000 products, including foods, medications, and cosmetics, it is impossible to completely eradicate them from daily encounters. Replication studies and long-term assays are required to decrease fear resulting from the limited research that currently exists.

References