The Potential Toxicity of Artificial Sweeteners

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ABSTRACT
Since their discovery, the safety of artificial sweeteners has been controversial. Artificial sweeteners provide the sweetness of sugar without the calories. As public health attention has turned to reversing the obesity epidemic in the United States, more individuals of all ages are choosing to use these products. These choices may be beneficial for those who cannot tolerate sugar in their diets (e.g., diabetics). However, scientists disagree about the relationships between sweeteners and lymphomas, leukemias, cancers of the bladder and brain, chronic fatigue syndrome, Parkinson's disease, Alzheimer's disease, multiple sclerosis, autism, and systemic lupus. Recently these substances have received increased attention due to their effects on glucose regulation. Occupational health nurses need accurate and timely information to counsel individuals regarding the use of these substances. This article provides an overview of types of artificial sweeteners, sweetener history, chemical structure, biological fate, physiological effects, published animal and human studies, and current standards and regulations.

Consumers and food manufacturers have long been interested in dietary sweeteners to replace sucrose in foods, enhancing flavor while reducing calories and the risk for dental caries. However, their safety has been controversial. Because Americans are concerned about the obesity epidemic in the United States, occupational health nurses are frequently asked about the safety of sugar substitutes. Recently these products have received increased attention because of their effects on glucose regulation. Occupational health nurses need accurate and timely information to appropriately counsel individuals who use these substances. This article provides an overview of the types of artificial sweeteners, sweetener history, chemical structure, biological fate, physiological effects, published animal and human studies, and current standards and regulations.

Artificial sweeteners have been classified as nutritive and non-nutritive depending on whether they are a source of calories. The nutritive sweeteners include the monosaccharide polyols (e.g., sorbitol, mannitol, and xylitol) and the disaccharide polyols (e.g., maltitol and lactitol). They are approximately equivalent to sucrose in sweetness (Dills, 1989). The non-nutritive sweeteners, better known as artificial sweeteners, include substances from several different chemical classes that interact with taste receptors and typically exceed the sweetness of sucrose by a factor of 30 to 13,000 times (Table 1).

Food additives are regulated by the Food and Drug Administration (FDA) under the Food, Drug & Cosmetic Act and its many amendments. The FDA reviews data on all new substances reasonably expected to become food components. The FDA may limit the form of a food additive in prepared foods or as tabletop sweeteners. The petitioner (manufacturer) is required to submit data to demonstrate the safety of the substance. However, a number of exclusions may impact artificial sweeteners. Compounds that were already on the list of substances...
considered generally recognized as safe (GRAS) or were otherwise approved prior to 1958 by the FDA are not officially recognized or regulated as food additives. In these cases, the burden is on the FDA to show that a substance is unsafe.

Typically, toxicological evidence is derived from studies in appropriate animal models, and possibly from human trials. The compounds can be evaluated across a wide range of exposures, including duration and persistence of exposures. Once the product is marketed, case reports and epidemiologic studies may identify other associated manifestations of toxicity in humans. Although the FDA often focuses on chronic toxicity encompassing effects on fertility, reproduction, fetal development, teratogenicity, carcinogenicity, and mutagenicity, an evaluation of acute effects on the nervous system, cardiovascular system, and other organ function is also needed. Epidemiologic evaluation or risk assessment requires

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Brand Names</th>
<th>FDA Approval</th>
<th>Number of Times Sweeter Than Sucrose</th>
<th>kcal/g</th>
<th>Commercial Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acesulfame-K</td>
<td>Sunett, Sweet One</td>
<td>1988—tabletop 1993—beverages 2003—general use, but not in meat or poultry</td>
<td>200</td>
<td>0</td>
<td>Baked goods, frozen desserts, candies, beverages, cough drops, breath mints</td>
</tr>
<tr>
<td>Alitame</td>
<td>Aclame</td>
<td>Pending</td>
<td>2,000</td>
<td>1.4</td>
<td>Baked goods, hot and cold beverages, milk products, frozen desserts and mixes, fruit preparations, chewing gums and candies, tabletop sweeteners, toiletries, pharmaceuticals</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>SugarTwin, Sucaryl</td>
<td>GRAS until banned in 1970</td>
<td>30</td>
<td>0</td>
<td>Tabletop sweetener, beverages</td>
</tr>
<tr>
<td>Neotame</td>
<td></td>
<td>2002</td>
<td>7,000–13,000</td>
<td>0</td>
<td>Baked goods, soft drinks, chewing gum, frosting, frozen desserts, jams, jellies, gelatins, puddings, processed fruit and fruit juices, toppings, syrups</td>
</tr>
<tr>
<td>Saccharin</td>
<td>Sweet’N Low, Sweet Twin, Necta Sweet</td>
<td>GRAS</td>
<td>200–700</td>
<td>0</td>
<td>Tabletop sweetener, baked goods, soft drinks, jams, chewing gum</td>
</tr>
<tr>
<td>Sucralose</td>
<td>Splenda</td>
<td>1998—in 15 food categories 1999—general-purpose sweetener</td>
<td>~600</td>
<td>0</td>
<td>Tabletop sweetener, beverages, chewing gum, frozen desserts, fruit juices, gelatins</td>
</tr>
</tbody>
</table>

*FDA = Food and Drug Administration; GRAS = generally recognized as safe.*
an accurate estimate of sweetener intake in the general population and particularly in individual subgroups compared to a standard level of intake (Tennant, 2002). The acceptable daily intake (ADI) levels for food additives are most often based on data derived from animal models for the “no observed adverse effect level” (NOAEL) with daily exposure.

According to a 2007 survey from the Calorie Control Council, 86% of Americans use low-calorie, reduced-sugar, or sugar-free foods and beverages (Calorie Control Council, 2007). To date, the FDA has approved five sugar substitutes for use in a variety of foods with another pending. In the United States, the three most common primary compounds used as sugar substitutes are saccharin (e.g., Sweet’N Low), aspartame (e.g., Equal and NutraSweet), and sucralose (e.g., Splenda). In many other countries, cyclamate and the herbal sweetener stevia are used extensively.

SACCHARIN

History

Saccharin, the first artificial sweetener, was discovered serendipitously, as were most artificial sweeteners. In 1879, Constantine Fahlberg was researching the oxidation mechanisms of toluenesulfonamide while working at Johns Hopkins University in the laboratory of Ira Remsen. During his research, a substance accidentally splashed on his finger; he later licked his finger and noticed the substance had a sweet taste, which he traced back to saccharin (Arnold, 1983). Since that time, a number of compounds have been discovered and used as food additives for their sweetener properties. Saccharin has been in use since 1900 and obtained FDA approval in 1970.

Saccharin has no calories and is 300 times sweeter than sugar (FDA, 2006). It is marketed as Sweet’N Low and sweetens various products, including soft drinks, baked goods, jams, chewing gum, canned fruit, candy, dessert toppings, and salad dressings. Saccharin is also used in cosmetic products (e.g., toothpaste, mouthwash, and lip gloss), vitamins, and medications.

Chemistry and Metabolism

Saccharin is formed by an initial reaction between toluene and chlorosulfonic acid. It is then converted to a sulfonamide with ammonia, then oxidized to a benzoic acid and heated to form the cyclic imide. Biologically, following ingestion, saccharin is not absorbed or metabolized. It is excreted, unchanged, via the kidneys. Because saccharin is not metabolized, the FDA considers this compound safe.

Toxicology

Exposure studies of saccharin provide both positive and negative results, including the potential to induce cancer in rats, dogs, and humans. A review by Arnold (1983) provided information on two-generation saccharin bioassays. Two-generation studies are beneficial in researching the potential effects of substances. For these studies, animals were exposed to the compound of interest, in this case saccharin, at all stages of development (i.e., in utero, during lactation, and in feed as an adult). At the time of Arnold’s publication, only three studies of saccharin used a two-generation model. These studies clearly demonstrated that when rats were exposed to diets containing 5% or 7.5% saccharin from the time of conception to death, an increased frequency of urinary bladder cancers was found, predominantly in males. It was noted that saccharin is not metabolized; it is nucleophilic and does not bind to DNA. However, it does suppress humoral antibody production in rats. At dosages of 5% or greater, saccharin does not act as a typical chemical carcinogen, according to the theory that all carcinogens are strong electrophilic agents (Arnold).

The results of the above study resulted in the prohibition of saccharin in Canada and a proposed ban in the United States (Arnold, 1984). This proposed U.S. ban was withdrawn in 1991, but foods containing saccharin were required to carry a warning label (International Sweeteners Association, 2008). This warning label was placed on all products containing saccharin to indicate “saccharin is a potential cancer causing agent.” Future research showing the safety of this product led to this decision being overturned in 2000 (Calorie Control Council, 2007). A ban on saccharin still exists in Canada; however, Health Canada is currently considering relisting saccharin as a food additive (Health Canada, 2007).

In 2004, Weihrauch and Diehl published a review of artificial sweeteners. They reported that more than 50 studies had been published about saccharin in laboratory rats. Their review of first-generation rats indicated that none of the groups demonstrated significantly more neoplasms in the saccharin-fed animals over controls. They cited a study by Fukushima et al. (1983) showing an increase in bladder neoplasms but continued to refute their results, stating the rats used in this trial were frequently infected with a urinary parasite that could have made the rats susceptible to bladder cell proliferation (Weihrauch & Diehl).

A case study of the hepatotoxicity of saccharin was published in 1994 (Negro, Mondardini, & Palmas). 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. Re-exposure to pure saccharin supported its role in pathogenesis of the liver damage (Table 2).

ASPARTAME

History

In 1965, a chemist at G. D. Searle was studying new treatments for gastric ulcers. To test new anti-ulcer drugs, the biologists used a tetrapeptide normally produced in the stomach. To synthesize this tetrapeptide, one of the steps in the process was to make an intermediate, aspartyl-phenylalanine methyl ester. Accidentally, a small amount of the compound landed on the chemist’s hand. Without noticing the compound, the chemist licked his finger and discovered a sweet taste. After realizing it was from the powder intermediate and believing it was not likely to be toxic, he again tasted the intermediate and found it was indeed sweet aspartame (Mazur, 1984).
Aspartame was first approved by the FDA in 1981 as a tabletop sweetener; in 1996, it was approved as a general-purpose sweetener in all foods and drinks (FDA, 2006). Since its approval, aspartame has been used in more than 6,000 products by hundreds of millions of people in countries all around the world (Butchko & Star-gel, 2001). It is 200 times sweeter than sucrose and is marketed under the brand names Equal and NutraSweet. Aspartame can be found in a wide variety of prepared foods (e.g., carbonated and powdered soft drinks, chewing gum, confections, gelatins, dessert mixes, puddings and fillings, frozen desserts, and yogurt), tabletop sweetener, and some medications (e.g., vitamins and sugar-free cough drops).

Chemistry and Metabolism

The dipeptide aspartame (L-aspartyl-L-phenylalanine methyl ester) has had an increasing market share and been the subject of continuing controversy. Because it contains phenylalanine, the FDA has mandated packaging bear a warning label to prevent individuals with the rare genetic disorder phenylketonuria from ingesting this substance. The Institute of Medicine’s Food and Nutrition Board has not issued upper tolerable intake levels for either aspartate or phenylalanine based on available data and models of chronic exposure (Institute of Medicine, 2005). Phenylalanine is an amino acid used as a building block for proteins. Individuals who suffer from phenylketonuria lack or have insufficient amounts of the enzyme phenylalanine hydroxylase, required to breakdown phenylalanine. Without the presence of this enzyme, phenylalanine accumulates. Phenylalanine buildup can significantly alter human brain function. All children are screened for this rare disorder in the United States.

Upon ingestion, aspartame is hydrolyzed in the intestinal lumen into its components, aspartic acid, phenylalanine, and methanol. These components are then absorbed into the blood and each is metabolized. It has been hypothesized that neither aspartame nor its components accumulates in the body. These components are used in the body in the same ways as when they are derived from common foods (Aspartame Information Center, 2006). Following a single aspartame dose of 34 mg/kg, 12 normal adults demonstrated no increase in plasma or red blood cell aspartate concentrations; however, phenylalanine concentrations doubled within an hour and returned to baseline.

### Table 2

**Toxic Potential of Artificial Sweeteners**

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Known Metabolites</th>
<th>ADI (mg/kg/d)</th>
<th>Manifestations of Toxicity in Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acesulfame-K</td>
<td>Methanol, aspartic acid, phenylalanine</td>
<td>15</td>
<td>Acute: Headache</td>
</tr>
<tr>
<td>Aspartame</td>
<td>Methanol, aspartic acid, phenylalanine</td>
<td>50</td>
<td>Chronic: Clastogenic, genotoxic at high doses, thyroid tumors in rats</td>
</tr>
<tr>
<td>Cyclamate</td>
<td>Cyclohexylamine</td>
<td>1</td>
<td>Acute: Headache, dry mouth, dizziness, mood change, nausea, vomiting, reduced seizure threshold, thrombocytopenia</td>
</tr>
<tr>
<td>Neotame</td>
<td>De-esterified neotame, methanol</td>
<td>2</td>
<td>Chronic: Bladder cancer in mice, testicular atrophy in mice</td>
</tr>
<tr>
<td>Saccharin</td>
<td>O-sulfamoylbenzoic acid</td>
<td>5</td>
<td>Acute: Headache, hepatotoxic at high doses</td>
</tr>
<tr>
<td>Sucralose</td>
<td></td>
<td>5</td>
<td>Chronic: Lower birth rate, weight loss (due to decreased consumption at higher doses)</td>
</tr>
</tbody>
</table>

**ADI = acceptable daily intake.**
in 4 hours (Stegink, Filer, & Baker, 1977). One of its metabolites, methanol, has been shown to further metabolize into formaldehyde and formic acid. The development of metabolic acidosis has occurred with significant blood levels of formic acid (Palese & Tephly, 1975).

Toxicology

By far, aspartame has been the most controversial artificial sweetener because of its potential toxicity. Numerous websites are devoted to removing aspartame from all sources immediately. Although some of these websites list relevant literature and demonstrate cause and effect, others attribute an all-inclusive disease list to the ingestion or absorption of aspartame.

New research from Soffritti et al. (2007) provides evidence of the carcinogenic potential of this compound. Their research, using Sprague Dawley fetal rats, has demonstrated a significant increase of malignant tumors in males, an increase in the incidence of lymphomas and leukemias in males and females, and an increase in the incidence of mammary cancer in females. These results reinforce and confirm previous research that also demonstrated the carcinogenicity potential of aspartame and the increased carcinogenic potential if exposure occurs during gestation. It is notable that the dosage tested approximated the ADI for humans.

In other published reports, Blumenthal (1997) reported three case studies wherein women ages 40, 32, and 26 all 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. Additionally, a case report in 2007 revealed four individuals with thrombocytopenia attributed to products containing aspartame (Roberts, 2007). This conclusion was based on recurrence of blood dyscrasia on two or more occasions after rechallenge, and the absence of any other definable factors. One of the reports was of a 10-year-old girl who developed a decline in platelet count to 1,000 cu/mm, coupled with enlargement of the liver and spleen, and a marked increase in histiocytes in the bone marrow. A dramatic clinical and hematological normalization followed when additives were eliminated from her diet. Similar recurrences were documented twice after ingesting aspartame. Remissions were maintained when the client abstained from aspartame products (Roberts).

In a newborn rodent model, hypothalamic neuronal necrosis due to dicarboxylic amino acids (i.e., the aspartic acid found in aspartame) was observed. However, this necrosis was not observed in a non-human primate model, even at 10-fold higher doses (Stegink, Shepherd, Brummel, & Murray, 1974; Stegink, 1976). The other amino acid found in aspartame, phenylalanine, is metabolized differently in rodents, so only data from primate animal models can be considered. Phenylalanine doses of 3,000 mg/kg/d in the first few years of life produced irreversible brain damage in monkeys (Waismann & Harlow, 1965). Unfortunately, no dose-response data are available for use in estimating human effects.

In humans, aspartame doses of 2 to 100 mg/kg resulted in dose-related increases in phenylalanine without an observed effect on behavior or cognitive performance (Filer & Stegink, 1988; Lieberman, Caballero, Emde, & Bernstein, 1988; Stokes, Belger, Banich, & Taylor, 1991). In sub-chronic dosing studies, aspartame doses of 30 to 77 mg/kg/d over 13 weeks in 126 children and adolescents and a similar study in young adults administered 36 mg/kg/d showed no significant impact on renal or hepatic function, hematologic status, ophthalmic examinations, or plasma lipid profile (Frey, 1976; Knopp, Brandt, & Arky, 1976).

ACESULFAME-K

History

Acesulfame-K (potassium) was discovered in 1967 by chemist Karl Clauss. He noticed a sweet taste when he licked his finger while working in the laboratory. Acesulfame-K was approved in the United States in 1988 for specific uses, including a tabletop sweetener. In 1998, the FDA approved acesulfame-K for use in beverages. In particular, it has been used to decrease the bitter aftertaste of aspartame and can be found in NutraSweet-containing products. In 2003, it was approved for general use in foods, excluding meat or poultry (FDA, 2006).

Acesulfame-K is 200 times sweeter than sugar and has no calories. Brand names include Sunett and Sweet One. It can be found in baked goods, frozen desserts, candies, beverages, cough drops, and breath mints.

Chemistry and Metabolism

Acesulfame-K is the generic name for the potassium salt of 6-methyl-1,2,3-oxathiazine-4(3H)-one-2,2, dioxide. The synergistic effect of acesulfame-K with glucose, fructose, sucrose, and sucralose increases its sweetness intensity (O’Donnell, 2005). Acesulfame-K is not metabolized by the body; it is excreted unchanged (Calorie Control Council, 2007).

Toxicology

Cyto genetic studies on mice that have ingested acesulfame-K have been published. One study (Mukherjee & Chakrabarti, 1997) of the cytogenicity of this sweetener indicated that when the dosage administered to mice was within the ADI of 15 mg/kg of body weight, the number of chromosomal aberrations was not significant compared to control mice. However, at higher doses (60, 450, 1,100, and 2,250 mg/kg), acesulfame-K was clastogenic and genotoxic. Therefore, their results demonstrate unequivocally that, depending on dose, acesulfame-K interacts with DNA to produce genetic damage. Additional studies on genotoxicity are recommended because of potential DNA interaction at high doses. However, doses capable of producing damage are well above the ADI.

SUCRALOSE

History

Sucralose was accidentally discovered in 1976 when Tate & Lyle, a British sugar company, was looking for
ways to use sucrose as a chemical intermediate. In collaboration with King’s College in London, halogenated sugars were being synthesized and tested. A graduate student misunderstood a request for “testing” of a chlorinated sugar as a request for “tasting,” leading to the discovery that many chlorinated sugars are sweet, with potencies some hundreds or thousands of times as great as sucrose (EdInformatics, 1999).

Sucralose is 600 times sweeter than sugar and contains no calories. Sucralose was approved by the FDA in 1998 for use in 15 food categories, including a tabletop sweetener under the brand name Splenda. It is used in beverages, chewing gum, frozen desserts, fruit juices, and gelatins. In 1999, the FDA expanded its use as a general-purpose sweetener in all foods.

Chemistry and Metabolism
Sucralose is a sucrose molecule in which three of the hydroxyl groups have been replaced by chlorine atoms. Although sucralose is made from table sugar, it adds no calories because it is not digested in the body. Most of the sucralose given orally to mice, rats, dogs, and humans passes through the gastrointestinal tract and is eliminated in the feces unchanged. Roberts, Renwick, Sims, and Snodin (2000) researched radioactive metabolites of sucralose in humans. Their research indicated sucralose was the principal component in the urine together with two additional polar components accounting for only 2.6% of the administered dose (range, 1.5% to 5.1% of dose). Both metabolites possessed characteristics of glucuronide conjugates of sucralose.

Toxicology
Toxicology studies of sucralose show little effect, the most significant finding being shrunken thymus glands with diets of 5% sucralose. Review and evaluation of the data, including a special immuno toxicity study, clearly demonstrated that thymic changes were not a manifestation of intrinsic toxicity, but rather an exacerbation of the normal process of involution resulting from a nutritional deficit to reduced food intake (Grice & Goldsmith, 2000).

Cases studies have been reported on sucralose consumption and the increased incidence of deleterious effects. Bigal and Krymchantowski (2006) discuss migraines triggered by sucralose. Multiple blinded posttests were provided for this client once she was migraine free to determine if sucralose was the trigger for her migraines. In all cases, on consumption of sucralose, her migraines returned. The client refused further participation in the study due to the migraines associated with the sucralose-containing test solution.

McLean Baird, Shephard, Merritt, and Hildick-Smith (2000) published a study of sucralose tolerance in humans. Sucralose was administered to eight individuals for up to 12-week intervals. They experienced no adverse health effects at doses up to 10 mg/kg/d and repeated doses increasing to 5 mg/kg/d for 13 weeks. Although an important study, it is limited by the number of participants and the length of postintervention study.

Neotame
History
Neotame is the newest artificial sweetener, a derivative of aspartame. Another similar compound, alitame, is pending approval before the FDA. Neotame is 7,000 to 13,000 times sweeter than sugar and has no calories. The FDA approved neotame in 2002 as a general-purpose sweetener, excluding in meat and poultry. It can be found in baked goods, soft drinks, chewing gum, frosting, frozen desserts, jams, jellies, gelatins, puddings, processed fruits, toppings, and syrups.

Chemistry and Metabolism
A t-butyl group is added to the free amine group of aspartic acid. This addition adds a second hydrophobic group and results in a product that is 30 to 60 times sweeter than aspartame (Nofre & Tinti, 2000). It is rapidly metabolized by hydrolysis of the methyl ester via esterases present throughout the body. This process yields des-esterified neotame, the major metabolite, and an insignificant amount of methanol. Neotame and de-esterified neotame are rapidly cleared from the plasma. It is completely eliminated from the body with recovery in urine and feces within 72 hours (European Food Safety Authority, 2007). Due to the presence of the 3,3-dimethylbutyl group, peptidases, which would typically break the peptide bond between the aspartic acid and phenylalanine moieties, are essentially blocked, thus reducing the availability of phenylalanine (Sweeteners Holdings, Inc., 2002).

Toxicity
Studies of neotame reveal changes in body weight, body weight gain, and food consumption. It is noted that these effects are not due to the toxic profile of neotame, but rather to the unpalatability of feeds containing this sweetener. Therefore, rats will decrease their daily food intake, resulting in long-term loss in body weight and less weight gain. In definitive safety studies, no adverse findings related to neotame treatment were found in clinical observations, physical examinations, water consumption, or clinical pathology evaluations; nor were there morbidity, mortality, organ toxicity, or macroscopic or microscopic postmortem findings (Mayhew, Comer, & Stargel, 2003).

Health Benefits from Artificial Sweeteners
Artificial sweeteners are present in many foods consumed by Americans. Their use is beneficial in that they provide sweetness, increasing the palatability of foods without the added sugar and resulting calories, an important adjunct to weight loss and diet regimens. Most artificial sweeteners are not metabolized by the body and are therefore considered safe. However, scientists disagree about safety because the metabolites of the “non-metabolized” compounds have been shown to produce deleterious effects in mice, rats, and dogs.

Health Effects Controversy
Many of the studies on product safety have been conducted by companies that produce these products and are
not generally available to consumers. A Medline search of publications from 2000 to 2008 using the key words “artificial sweeteners,” “sweetening agents,” “toxicity,” “toxicology,” “safety,” and “consumer product safety” resulted in only one study available to readers of primary product safety data. Groups that believe the safety of these substances has not been demonstrated point to the length of studies, sample sizes, and lack of controls.

ARTIFICIAL SWEETENERS AND METABOLISM

Several recent studies have focused on the effects of artificial sweeteners on metabolic systems, especially in individuals with diabetes. In 2007, Ferland, Brassard, and Poirier investigated the effect of aspartame on plasma glucose and insulin levels during acute exercise in 14 men with type 2 diabetes. Contrary to all expectation, the aspartame breakfast induced a similar rise in glucose and insulin levels at baseline as the sucrose meal. It would be beneficial to design similar studies to support or challenge their findings. According to the data presented in this study, it would be damaging for diabetics to continue consumption of the sugar-free substitute if the product actually elevates blood glucose levels.

A 2007 article by Gallus et al. discussed artificial sweeteners and associated cancer risks. The authors reviewed several case-control studies and found a lack of association between saccharine, aspartame, and other sweeteners and several common neoplasms. They did cite an ecology study that indicated a direct correlation between brain cancer and aspartame consumption. These studies are subject to ecological fallacy and the hypothesis was not confirmed in animal or human studies.

ACCEPTABLE DAILY INTAKE

Standards and regulations have been set by the United States and other countries whose citizens consume large quantities of artificial sweeteners. ADIs are calculated according to current safety research. The ADI is defined as an intake that “individuals in a (sub)population may be exposed to daily over their lifetimes without appreciable health risk” (World Health Organization, 2004, p. 10). The ADI is calculated by dividing the maximum dose at which a study has not shown a negative effect in animal studies. For example, if a study revealed a 500-mg dose did not produce toxic effects in animals, this number is divided by 100 to calculate the ADI. The calculated result of 5 mg is the ADI.

ADIs for various substances can change with the advent of additional research warranting a reduction. Also, it is possible that studies may provide sufficient evidence for the product to be removed from the marketplace entirely. Cyclamate is one example of removal; this artificial sweetener was banned from the U.S. market in 1970 after several experimental studies on rats demonstrated its carcinogenic potential.

The ADI for saccharin is currently 5 mg/kg of body weight per day. The ADI for acesulfame-K for both the FDA and the Joint Expert Committee for Food Additives (JECFA) is 15 mg/kg of body weight per day. The European Union (EU) reevaluated this sweetener and supports its safety, but recommended an ADI of 9 mg/kg/d. The ADI for sucralose is 5 mg/kg/d. In 2002, the FDA set the ADI for neotame at 18 mg/kg/d. The JECFA confirmed the safety of neotame in 2003 and granted an ADI of 2 mg/kg/d (American Dietetic Association, 2004).

Aspartame has an ADI of 50 mg/kg/d in the United States and 40 mg/kg/d in the EU (Soffritti et al., 2007). This translates into a 150-pound (70-kg) person consuming nearly twenty 12-ounce cans of soft drinks sweetened with aspartame every day over a lifetime (Beverage Institute for Health & Wellness, 2006). This limit is not difficult to achieve, considering the volume of Biggie Size and Big Gulp sodas, each containing 42 and 44 ounces, respectively, or 5.5 servings per day or 3.5 2-liter sodas per day. This quantity does not take into account other sources of aspartame ingested daily through tabletop sweeteners and other artificially sweetened foods.

SUSCEPTIBLE POPULATIONS

Susceptible populations for the potential deleterious effects of artificial sweeteners include diabetics, children, pregnant women, women of childbearing age, breastfeeding mothers, individuals with low seizure thresholds, and individuals at risk for migraines. More studies are required for these susceptible populations. A focus on children is important because they have a higher intake of foods and beverages per kilogram of body weight (Renwick, 2006). Also, more research on the effect of artificial sweeteners on diabetic clients is needed because this population is likely to ingest larger quantities of sugar substitutes.

Because artificial sweeteners are in more than 6,000 products, including foods, medications, and cosmetics, it is impossible to completely eradicate them from daily encounters. Controversy exists over the toxicity of the artificial sweeteners presented in this article. Replication studies and long-term assays are required to decrease fear resulting from the limited research that currently exists.

IMPlications FOR PRACTICE

Alarmingaly, the rate of obesity in the United States continues to rise. The Centers for Disease Control and Prevention reported in 2006 only 4 states had a prevalence of obesity less than 20%. 22 states had a prevalence equal to or greater than 25% and 2 of these states had a prevalence equal to or greater than 30% (Centers for Disease Control and Prevention, 2007). Counseling of individuals in primary care settings, schools, and workplaces is of increasing importance. Nurses need up-to-date, evidence-based information to guide the messages they give to obese individuals or individuals interested in controlling their weight. Occupational health nurses play an important role in dissemination of dietary and weight-loss information.

To aid in battling obesity, many individuals use low-calorie artificial sweeteners as a substitute for high-calorie foods. The American Dietetic Association states their position on the use of non-nutritive sweeteners, indicating consumers can enjoy these substances when consumed in a diet guided by current federal nutrition recommenda-
IN SUMMARY

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1 Artificial sweeteners provide the sweetness of sugar without the calories. Five Food and Drug Administration-approved sugar substitutes currently exist. Most of these substitutes provide 0 kcal/g.

2 Some research has associated artificial sweeteners with health conditions such as cancers, hepatotoxicity, migraines, and low birth weight. Much controversy concerning this issue still exists. This research has been disputed and some studies have demonstrated the safety of these sweeteners.

3 Occupational health nurses can educate clients regarding the risks and benefits of artificial sweeteners. They can also promote exercise and healthy eating habits for individuals who may consider consuming artificial sweeteners.

For individuals planning to start dieting, the nurse should provide information about decreasing the number of calories consumed daily as well as introducing physical activity under the guidance of a health care provider. When nurses discuss the benefits of artificial sweeteners, it is important to be clear that although these substances will aid in decreasing the number of calories consumed, little research has shown their efficacy for weight loss. Additionally, potential deleterious side effects may be associated with their use.

Use of artificial sweeteners during pregnancy should be restricted due to the limited research available surrounding this topic. The maternal diet is important to the growing fetus. Sedova et al. (2007) indicate that growing evidence suggests fetal and early life environments are determinants of disease in adulthood, including dyslipidemia, insulin resistance, obesity, and hypertension. Their studies on early life exposure to a sucrose-rich diet in rats resulted in distinct responses to long-term postnatal high sucrose feedings. Additionally, the offspring of the sucrose-fed mothers displayed higher adiposity and substantial increases in triglyceride liver content together with unfavorable distribution of cholesterol into lipoprotein subfractions. Saccharin has been shown to cause effects such as depressed growth; anemia; iron, vitamin A, and folate deficiency; and elevated vitamin E in rats (Garland et al., 1993). Nurses can educate women of childbearing age and pregnant and lactating women to consume these substances in moderation or not at all.

The use of artificial sweeteners remains controversial. Their consumption has been shown to cause mild to serious side effects ranging from nuisance headaches to potentially life-threatening cancer. Recent reports of selected sweeteners suggest they are not efficacious in weight loss and may promote weight gain (Swithers & Davidson, 2008). Much literature is available on artificial sweeteners; however, it is difficult for the general public to decipher the research, especially when researchers themselves disagree. Occupational health nurses and other health care providers should be aware of current research surrounding the use of artificial sweeteners and inform clients of the potential risks associated with their use.

REFERENCES
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