Canadian Diabetes Association National Nutrition Committee Technical Review: Non-nutritive Intense Sweeteners in Diabetes Management

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ABSTRACT

The current Canadian Diabetes Association Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada state that up to 10% of daily calories can be derived from sugars. However, individuals with diabetes may also be relying on alternative, low-calorie sweetening agents (providing little or no calories along with sweet taste) to control carbohydrate intake, blood glucose, weight and dental health. Most low-calorie sweeteners, sometimes called intense or artificial sweeteners, are classified and regulated as food additives with set acceptable daily intake (ADI) levels. The Health Canada Health Products and Food Branch approved intense sweeteners for table-top use and as additives in products such as soft drinks, chewing gum, fruit and fruit spreads, dairy products and desserts. This technical review summarizes the literature on the potential health benefits and risk associated with the consumption of non-nutritive intense sweeteners (excluding polyols) and the evidence for the safety of intense sweetener use among individuals with diabetes and their effects on glycemia, appetite, weight, blood lipids, blood pressure and renal function. Research

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Keywords: acesulfame potassium (acesulfame-K), aspartame, cyclamate, non-nutritive sweetener, saccharin, sucralose, stevia, tagatose, thaumatin

RÉSUMÉ

Selon les Lignes directrices de pratique clinique actuelles de l'Association canadienne du diabète, jusqu'à 10 % des calories consommées chaque jour peuvent provenir des sucres. Cependant, les personnes atteintes de diabète peuvent aussi se servir de succédanés contenant peu ou pas de calories et ayant le goût du sucre pour limiter leur consommation de glucides, maîtriser leur glycémie et leur poids et éviter les caries dentaires. La plupart des édulcorants à faible teneur en calories, parfois appelés édulcorants de synthèse ou édulcorants artificiels, sont considérés comme des additifs alimentaires et leur apport quotidien est par conséquent réglementé. La Direction générale des produits de santé et des aliments de Santé Canada approuve l'utilisation des édulcorants de synthèse à table et comme additif dans divers produits tels les boissons gazeuses, la gomme à mâcher, les fruits et fruits à tartiner, les produits laitiers et les desserts. Cette analyse technique résume les publications sur les avantages et les risques possibles pour la santé des édulcorants de synthèse non nutritifs (sauf les polyols), les données sur l'innocuité des édulcorants de synthèse chez les personnes atteintes de diabète et leurs effets sur l'équilibre de la glycémie, l'appétit, le poids, les lipides sanguins, la tension artérielle et la fonction rénale. La recherche sur les effets, avantages et risques métaboliques possibles des édulcorants de synthèse chez les personnes atteintes de diabète, les enfants, les adolescents et les femmes enceintes ou qui allaitent a été évaluée afin que des recommandations factuelles puissent être faites au sujet de leur consommation par les personnes atteintes de diabète. Les données actuelles ne corroborent pas ce que les publications médicales véhiculaient dans le passé, c'est-à-dire que les édulcorants à faible teneur en calories stimulent l'appétit ou perturbent les mécanismes qui régissent la faim et la satiété. Il semble en effet que la consommation quotidienne (jusqu'à concurrence de l'apport quotidien acceptable) d'aspartame, de sucralose, de saccharine, de cyclamate et de D-tagatose n'a pas d'effet significatif sur la glycémie ou les lipides sanguins chez les personnes atteintes de diabète. Les

investigating the potential metabolic effects, benefits and risk of intense sweetener use among individuals with diabetes, children and adolescents, and pregnant and lactating women was reviewed to draft evidence-based recommendations for their use by people with diabetes. Current evidence does not support an earlier belief, reported in the medical literature, that low-calorie sweeteners stimulate appetite or affect mechanisms that regulate hunger and satiety. Evidence indicates that daily consumption (up to ADI levels) of aspartame, sucralose, saccharin, cyclamate and D-tagatose has no significant effect on glycemic control or blood lipids in persons with diabetes. Current evidence indicates that intense sweeteners, used as an adjunct to multidisciplinary programs, may improve weight loss and weight control in obese persons. Consumption of intense sweeteners by older children and adolescents is unlikely to exceed ADI levels. Aspartame consumption below ADI levels has no effect on behaviour in children. In pregnancy, saccharin and cyclamate are not recommended, while other intense sweeteners have not been shown to be unsafe during this time. Intense sweeteners are most beneficial when they are used to replace energy-dense and nutrient-diluted foods including sucrose, and are least beneficial when used to displace nutrient-dense foods such as milk, fruits and fruit juices.

données actuelles indiquent que la consommation d'édulcorants de synthèse, ajoutée à des programmes multidisciplinaires, peut accélérer la perte de poids et améliorer la maîtrise du poids chez les personnes obèses. Il est peu probable que la consommation d'édulcorants de synthèse par les enfants plus âgés et les adolescents dépasse l'apport quotidien acceptable. La consommation de quantités d'aspartame inférieures à l'apport quotidien acceptable n'a pas d'effet sur le comportement des enfants. Pendant la grossesse, la consommation de saccharine et de cyclamate n'est pas recommandée, mais les autres édulcorants de synthèse ne se sont pas révélés nocifs pendant la grossesse. Les édulcorants de synthèse sont le plus profitables lorsqu'ils sont utilisés pour remplacer les aliments à haute teneur énergétique et à faible valeur nutritive, y compris le saccharose, et le moins profitables lorsqu'on s'en sert pour remplacer des aliments à grande valeur nutritive tels que le lait, les fruits et les jus de fruits.

INTRODUCTION

Traditionally, sucrose has been the most frequently used sweetener; however, recent data show that consumers are relying on alternative sweetening agents. This change in consumption patterns reflects concern about weight gain and the negative impacts sucrose and fructose may have on chronic disease, dental caries and/or glycemic control (1). A variety of high-intensity, non-nutritive sweeteners are currently available in Canada for use in select foods and food categories. These artificial sweeteners, most of which are many times sweeter than sucrose, have enabled consumers to satisfy their desire for sweetness without adding extra calories. Moreover, these sweeteners often appeal to individuals with diabetes who are attempting to modify carbohydrate intake to regulate blood glucose (BG), triglyceride (TG) concentrations and energy intake. Many healthcare professionals have voiced concern about the potential high use of intense sweeteners by individuals with diabetes.

METHOD

The National Nutrition Committee (NNC) of the Canadian Diabetes Association (CDA) systematically reviewed the scientific evidence regarding potential benefits and risk associated with the use of high-intensity sweeteners by adults with diabetes, children, adolescents, and pregnant and lactating women. This review focuses on high-intensity sweeteners that are: 1) available for general use (aspartame, acesulfame potassium [acesulfame-K], sucralose); 2) available for restricted use or pending for general use (saccharin, cyclamate, thaumatin); and 3) not currently approved for use as sweeteners in Canada (D-tagatose, stevia, alitame) (Table 1). Relevant peer-reviewed articles were assigned a level of evidence according to the methods used by the CDA Clinical Practice Guidelines Expert Committee in the CDA 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (2). The authors drew conclusions based on the evidence and relevance of the findings to the Canadian population. These evidence-based messages on the use of these sweeteners by individuals with diabetes were then assigned a grade as indicated in the system used for the CDA's clinical practice guidelines (2) (Table 2, Table 3). If there was no supportive Level 1, 2 or 3 evidence, or the conclusion was based on the consensus of the NNC, the assigned grade was D.

INTAKE OF HIGH-INTENSITY SWEETENERS

Few sweetener intake studies have been performed on the general population, and even fewer have been specifically designed to investigate intake in adults and children with diabetes. Of the studies published, none included Canadian data, which raises problems of interpretation in a Canadian context because Canadian regulatory approval differs from those countries in which the studies were conducted. Also, seasonal consumption in Canada and those countries may differ. Studies published in the last 8 years in Sweden (in adults

Table 1. Characteristics of non-nutritive sweeteners

Sweetener	*Sweetness (compared with sucrose)*	*ADI (mg/kg of body weight)*	*Commercial name*	*Regulatory status*	*Advantages*	*Limitations*
Acesulfame-K	200X	0–15*	Sunett®	Approved for use in foods under food and drugs regulations. Approved as general all-purpose table-top sweetener.	Non-carcinogenic, heat stable, synergistic sweetening relationship with other sweeteners, flavour enhancer.	High concentrations may leave a slight aftertaste.
Alimate	2000X	N/A (estimated 0.34)	N/A	Provision has not been established for addition to foods in Canada.		May emit 'off' flavour in acidic solution with high temperature. Limited experimental data in humans.
Aspartame	180X	0–40* 0–50**	Equal® NutraSweet®	Permitted for use as a food additive in Canada since 1981 in a number of foods including soft drinks, desserts, breakfast cereals, chewing gum. Also available as a table-top sweetener.	Non-carcinogenic, no aftertaste, causes no glycemic response.	Heat sensitive, limited shelf life at high pH, PKU safety issue—loses sweetness at alkaline pH. Health Canada requires a statement on any part of the label that aspartame contains phenylalanine.
Cyclamate	30–50X	0–11*	Sugar Twin® (Canada)	May be sold for direct consumer use, under specified conditions.	Heat stable, pleasant taste, appropriate for cooking, synergistic action when combined with other sweeteners.	Safety concerns: Health Canada requires that a statement appears indicating that the sweetener should only be used on the advice of a physician.
D-tagatose	92%	N/A	N/A	Provision has not been established for addition to foods in Canada.		
Saccharin	300–500X	0–5*	Sweet'N Low® Sugar Twin® (United States) Hermesetas®	Only available to general public from a pharmacy.	Heat stable, causes no glycemic response, synergistic sweetening relationship with other sweeteners.	Aftertaste, safety concerns about unproven association with lower urinary tract cancer.
Stevia (stevioside)	100–150X	N/A	N/A	Provision has not been established for addition to foods in Canada.	Potential role in regulation of hypertension, heat stable, somewhat resistant to acid hydrolysis, nonfermentable, odourless white powder, licorice-like aftertaste.	Requires clinical trials to demonstrate efficacy in those with diabetes. Although there are few studies, there is no evidence of a safety concern.
Sucralose	600X	0–15* 0–9 (in Canada)	Splenda®	Approved for use in foods under food and drugs regulations. Approved as general all-purpose table-top sweetener.	Heat and pH stable, non-carcinogenic, causes no glycemic response.	
Thaumatin	2000–3000X	Not specified	Talin®	Approved for use in chewing gum, breath fresheners, salt substitutes.	Flavour enhancer, masks bitterness of foods, adds palatability.	Limited experimental data in humans, leaves licorice aftertaste in high doses.

*According to the Joint Expert Committee of Food Additives, United Nations and World Health Organization
**According to the United States Food and Drug Administration

ADI = acceptable daily intake
N/A = not available
PKU = phenylketonuria

with and without diabetes, using self-administered questionnaires [3]), France (in children with type 1 diabetes, using 5-day food records [3]), Italy (in children using 14-day food records [4]), and Brazil (in adults with and without diabetes, using self-administered questionnaires [5]) will be used to discuss the intake of specific sweeteners in adults, children and individuals with diabetes.

All studies reported a high consumption of foods and beverages containing intense sweeteners (4), with major sources being beverages and table-top powder (5,6). One study, which compared intake in subjects with and without diabetes, reported a higher intake in those with diabetes (5). The estimated intake of aspartame by adults with (6) and without diabetes (4) and children (6) was not found to exceed the acceptable daily intake (ADI) defined by the country. As well, the estimated daily intake of acesulfame-K, cyclamates and saccharin by adults did not exceed the ADI (5). Although most studies reported the intake of acesulfame-K by children to be below the ADI (6), the Swedish study, using worst-case calculations, concluded that high intakes (169% of ADI) were found in some young children. Similarly, in this same study children had an unexpectedly high intake of table-top sweeteners (cyclamate) and the highest estimated (worst case) intake of cyclamate (317% of ADI) (4). The intake of cyclamate by adolescents in Italy did not exceed the ADI (6). In Sweden, childrens' estimated intake of saccharin only slightly exceeded the ADI (4), but Italian children's intake was below the ADI (6).

While many papers report that people with diabetes tend to consume, on average, more intense sweeteners than other groups in the population (7-15), data to support this are sparse. Children with diabetes are considered to constitute a group with a high consumption of sweeteners. However, the French study performed in children with type 1 diabetes (across 5 age groups) concluded that it was unlikely that total exposure to artificially sweetened foods and table-top sweeteners could rise above the European ADI (3).

Table 2. Criteria for assigning levels of evidence to published studies of treatment and prevention (2)

Level	*Criteria*
Level 1A	• Systematic overview or meta-analysis of high-quality, randomized, controlled trials. • Appropriately designed randomized, controlled trial with adequate power to answer the question posed by the investigators.
Level 1B	• Nonrandomized clinical trial or cohort study with indisputable results.
Level 2	• Randomized, controlled trial or systematic overview that does not meet Level 1 criteria.
Level 3	• Nonrandomized clinical trial or cohort study.
Level 4	• Other.

SAFETY OF HIGH-INTENSITY SWEETENERS

Extensive toxicity databases are available on each of the sweeteners currently available in Canada, and have been assessed by both national and international regulatory authorities. Based on the scientific evidence, Health Canada has set ADI levels for each of the approved non-nutritive sweeteners (Table 1). An ADI is defined as "the amount of a food additive, corrected for body weight, that can be ingested daily over a lifetime without appreciable health risk" (16). The calculation of ADI for human intake employs a large safety factor, generally 100-fold, applied to the no-effect dose. A no-effect dose of 100 mg/kg body weight of the studied animal would translate into 1 mg/kg body weight in humans. Someone consuming twice the ADI would still benefit from a safety factor of 50.

Aspartame

Aspartame (L-aspartyl-L-phenylalanine methyl ester), a dipeptide sweetener (8), has been available in Canada since 1981, and is currently allowed for use in table-top sweeteners, breakfast cereals, carbonated beverages and beverage mixes, dessert products, chewing gum, breath fresheners, fruit spreads, salad dressing, condiments and confectioneries (17). Aspartame is metabolized in the small intestine by the action of enterases and peptidases that hydrolyze aspartame to yield methanol and the 2 amino acids aspartic acid and phenylalanine (1,9,14). The metabolism of the sweetener provides approximately 4 kcal/g of energy. However, the energy added to the diet is negligible, as aspartame is 160- to 220-times sweeter by weight than sucrose and comparatively little is needed to achieve sweetness comparable to sucrose.

The safety of aspartame and its metabolic constituents has been established and continues to be critically and comprehensively monitored through extensive toxicology studies in laboratory animals, using much greater doses than people could possibly consume (18). Its safety has been further confirmed through studies in several human subpopulations, including: healthy infants, children, adolescents and adults; obese individuals with or without diabetes; lactating women; and individuals heterozygous for the genetic disease phenylketonuria (PKU), who have a decreased ability to metabolize phenylalanine (18). Although people with PKU

Table 3. Criteria for assigning grades of recommendations for clinical practice guidelines (2)

Grade	*Criteria*
Grade A	• The best evidence was at Level 1.
Grade B	• The best evidence was at Level 2.
Grade C	• The best evidence was at Level 3.
Grade D	• The best evidence was at Level 4 or consensus.

have been shown to tolerate small amounts of aspartame (<45 mg/kg/day) (19,20), its consumption is generally discouraged by healthcare professionals so as to not displace phenylalanine-containing, nutrient-rich foods. An early report on the safety of aspartame by Bradstock and colleagues (21), based on consumer complaints (n=231) reported to the United States (US) Food and Drug Administration (FDA), concluded that reported symptoms were mild and could not be associated with a single food item. However, in the US, a database is maintained by the Centers for Disease Control and Prevention and the FDA, in conjunction with The NutraSweet Company, to record all adverse incidences (major and minor) reported by consumers after ingesting foods containing aspartame (1,22).

Olney and colleagues (23) published a controversial correlative analysis suggesting that an increase in the incidence of brain tumours in industrialized countries may be linked to aspartame consumption. This study has been criticized for implying a cause-and-effect relationship from epidemiological studies and for drawing conclusions from a relationship assessed over a short period of time (8,24). A subsequent case-control study investigating the relationship between aspartame consumption and brain tumours in children did not find a relationship in children or an increased risk associated with maternal consumption during pregnancy (25).

Aspartame has also been implicated anecdotally in seizure provocation. However, a randomized, double-blind, placebo-controlled, crossover study of 18 individuals (16 adults, 2 children) who reported that their seizures were provoked by aspartame consumption concluded that an acute dosage of approximately 50 mg/kg was no more likely than placebo to cause seizures in these individuals (26). An earlier randomized, double-blind, placebo-controlled, crossover study concluded that aspartame, even when consumed at >10 times usual consumption, had no effect on the cognitive and behavioural status of children with attention deficit disorder (27) or biochemical or neurological activity in children with well-documented seizures (28). At this time, there is no scientific evidence to support the negative health effects that have been ascribed to aspartame.

Several safety issues continue to be raised about aspartame. These are derived from a concern about theoretical toxicity from its metabolic components—aspartate, phenylalanine and methanol. Interestingly, dietary exposure to these components by the population is much greater than from aspartame consumption (18). It has been proposed that consumption of aspartame could increase phenylalanine levels in blood, which would compete successfully with transporters into the brain and increase brain phenylalanine concentration, thereby affecting neurotransmitter synthesis (8,29,30). A deficit of alpha-aspartyl-phenylalanine (alpha-Asp-Phe) hydrolase activity has also been suggested as a cause of possible adverse effects of aspartame ingestion. A study of 48 children, described by their parents as sensitive to sugar, were fed diets high in sucrose, aspartame or saccharin for 3 successive 3-week periods. Alpha-Asp-Phe concentrations were below detection limits in all blood samples collected before and after consumption of the sweeteners. Phenylalanine and aspartic acid concentrations remained within normal limits and the activity of alpha-Asp-Phe hydrolase did not differ among groups (31), indicating that ingestion of aspartame had no effect.

Although intriguing biologically, there is currently no experimental support (animal or human) for an effect of aspartame consumption on any aspect of neurological function assessed (cognitive performance, mood or behaviour) (18). Randomized, double-blind, controlled clinical trials (albeit with relatively few subjects and for short feeding periods) have consistently shown that aspartame is no more likely than placebo to induce headaches (n=40) (32), allergic reactions (n=12, n=21) (22,23) or seizures (n=18) (26) in individuals who claim to have a sensitivity to aspartame or foods containing aspartame. In the largest of these studies, 61 self-reported "aspartame sensitive" individuals used a combined single-blind, double-blind, placebo-controlled design and could not reproduce any adverse neurological reactions to aspartame (22).

These clinical studies are not without limitations; sample sizes are small (due to the difficulty of recruiting subjects who had had reactions) and study periods relatively short (26,32-35). The ongoing scientific and public concern regarding aspartame has resulted in additional research, including evaluations of possible associations between aspartame and headaches, seizures, behaviour, cognition and mood, as well as allergic-type reactions and use by potentially sensitive subpopulations. Interestingly, the author of the largest of these negative-effect studies concluded that some individuals may indeed experience high sensitivity to aspartame (22). If a person claims to suffer from adverse effects after consuming aspartame, their claim should be taken seriously and other potential causes investigated (34).

Acesulfame potassium

Acesulfame potassium (acesulfame-K) (5,6-dimethyl-1,2,3-oxathizaine-4(3H)-one-2,2-dioxide) was approved by Health Canada in 1988 as a non-nutritive table-top sweetener for general purposes. It is often combined with other intense sweeteners, such as aspartame, to intensify its sweetness potential and decrease its bitter taste (14). Acesulfame-K is absorbed by the gut and excreted in the urine without being metabolized and is therefore not a source of energy (35). In 1983, the Joint Expert Committee of Food Additives of the Food and Agriculture Organization of the United Nations and the World Health Organization published an extensive review of studies addressing the safety of acesulfame-K and concluded that there was no evidence to suggest that it was not safe if consumed at or below the ADI (36). Ongoing monitoring of the safety of this and other sweeteners is

performed by a Food Safety Department, World Health Organization committee; their most recent report concludes that when consumed at or below the ADI, there is no evidence that it is unsafe to the general population or specific groups within the population (17).

Sucralose

Sucralose (1,6-dichloro-1,6-dideoxy-beta-D-fructofuranosyl-4-chloro-4-deoxy-alpha-D-galactopyranoside) has been available commercially in Canada since 1992 under the trade name Splenda®. Sucralose is synthesized by replacing 3 of the hydroxyl groups in sucrose with chlorine. Commercially, sucralose is combined with maltodextrin, which enables it to physically replace sucrose (37). Sucralose is not hydrolyzed in the intestine and less than 25% of an oral dose is absorbed. The small proportion that is absorbed is not metabolized and is excreted unchanged in the urine (37).

Studies investigating the safety of acute and chronic consumption of sucralose at ADI levels have not reported any adverse effects on human (38,39) or animal health (40-44). Sucralose was well tolerated by human volunteers (no clinical or metabolic changes were found) in single doses up to 10 mg/kg and repeated doses increasing to 5 mg/kg/day for 13 weeks (38). Fasting and 2-hour post-dosing blood sucralose concentrations obtained daily during week 12 of the study revealed no rising trend for blood sucralose (38). There were no clinically detectable adverse effects from sucralose intake in either study. Studies have confirmed that sucralose is noncariogenic (45). However, sucralose-based sweeteners that contain bulking ingredients to allow them to pour and measure like sugar do have cariogenic potential (although much lower than sugar) due to the presence of added carbohydrate fermented by bacteria in the mouth (45,46).

Saccharin

Saccharin, a coal tar derivative initially synthesized in 1879, was the first non-nutritive sweetener to be commercially available in North America. Saccharin is absorbed but not metabolized by the body and is excreted in the urine (35). Significant concerns have been raised about the safety of this sweetener. The primary concern was based on laboratory rodent studies that clearly demonstrated an increased incidence of bladder cancer when rats were fed high amounts of sodium saccharin in their diet from birth (47-49). In 1977, the Canadian Health Protection Branch, Health Canada, and the FDA banned the addition of saccharin to commercially available foods and beverages (47). In Canada, saccharin is available only in the form of a table-top sweetener from pharmacies (17). Since the original removal of saccharin from foods, a number of case-control studies have examined the association between saccharin and cancer (50). Collectively, these studies do not support a relationship between lower urinary tract cancer and the consumption of saccharin (51-54). The original studies in rodents have been challenged for their use of very high doses of saccharin and more recently because of information that the risk of cancer in rodents may be different from that of humans due to the inter-species differences in both toxicokinetics and toxicodynamics (15). Thus, in 1991, the FDA withdrew its ban on saccharin (14), but in Canada, saccharin remains in the restricted use category.

Cyclamates

Cyclamates consist of 3 closely related chemical forms: cyclamic acid, calcium cyclamate and sodium cyclamate. Based on studies demonstrating that feeding a mixture of saccharin and cyclamate (10:1, cyclamate:saccharin) results in cancer in laboratory rodents, the FDA withdrew permission to add cyclamates to foods in 1969. Since 1970, cyclamates have been available in Canada only as a table-top sweetener. Systematic reviews of the scientific literature by both the Cancer Assessment Committee of the FDA and the National Academy of Sciences have reversed the original conclusion that cancer risk is associated with consumption of cyclamate (55). Cyclamates are currently approved for use in foods in approximately 50 countries, but not Canada or the US (14). Further studies on the metabolism of cyclamates in humans and assurance of low risk of adverse health effects are required before the Health Canada's Health Products and Food Branch (HPFB) or the FDA will allow widespread use of this sweetener in foods. This decision is based on studies demonstrating that, in some individuals, cyclamates are not completely metabolized and can be converted to cyclohexylamine, a potential carcinogen (56) that may also have adverse cardiovascular effects (57).

Thaumatin

Thaumatin is one of 6 known naturally occurring intensely sweet-tasting plant proteins. Thaumatin, isolated from the West African plant *Thaumatococcus daniellii* (58,59), is approved for use in Canada only in chewing gum, breath fresheners, flavour enhancers and salt substitutes (17). Similar to any protein, thaumatin is digested to its constituent amino acids in the gastrointestinal (GI) tract prior to absorption (35). Very few clinical trials have been performed, but animal studies suggest that it is safe for human consumption (58).

D-tagatose

D-tagatose is a stereo-isomer of D-fructose that occurs naturally in various foods, including dairy products (e.g. cheese and yogurt). It is used as a low-calorie, full-bulk sweetener in cakes, frosted cereals and ice cream. D-tagatose has approximately 92% of the sweetening capacity of sucrose and is therefore not technically an intense sweetener. However, due to its decreased absorption in the small intestine and inefficient metabolism in the liver, its intake results in a substantially lower energy contribution per gram than sucrose (60-63).

Animal studies have demonstrated that, once absorbed, D-tagatose is metabolized in the liver (60-62). Long-term consumption of D-tagatose resulted in glycogen-induced liver enlargement in rats (without corresponding histopathology) (64); however, there is no evidence of this effect in humans (65,66). No adverse effects were seen on reproductive performance in rats given D-tagatose, or on fetal weight, sex distribution, liver weight, or external, skeletal and visceral malformations in the fetus when consumed at high levels by pregnant rats (64). In humans, passage of D-tagatose into the colon resulted in microbial fermentation (67), and consumption of a large, single daily dose of D-tagatose (30 g) was reported to increase flatulence and other minor GI disturbances (68). The frequency and severity of these GI disturbances were reported to increase with the dose. Despite this, studies in ileostomy patients have demonstrated that malabsorption of this sugar may have only a minor influence on the apparent absorption of other nutrients (63). D-tagatose has recently attained Generally Recognized As Safe (GRAS) status under FDA regulations, thereby permitting its use as a sweetener in foods and beverages in the US but not in Canada (69).

Stevia

The herb stevia (*Stevia rebaundiana*, Bert, Bertoni) is a traditional sweetener used in beverages in South America. Stevia sweetener is a mixture extracted from the leaves of the herb and consists mainly of the glycosides (stevioside) of the diterpene derivative steviol (70,71). Stevioside has been approved for more than 20 years for use as a sweetener in Japan, and does not appear to be cariogenic (72). Rodent studies have demonstrated that a portion of stevioside is absorbed and degraded to steviol, which appears to undergo further metabolism (73). Other studies indicate that a portion of stevia is metabolized by the intestinal microflora (70,71). The few studies in humans suggest a similar pattern of absorption and metabolism (70,71). Although animal studies have not associated stevioside consumption with adverse effects or toxicities (74,75), the limited data available on its metabolism and safety in humans have not enabled the HPFB to approve its use as a non-nutritive sweetener. Only the herb form of the plant is allowed for use in foods as a flavour enhancer and as a tea (17).

Alitame

Alitame is a protein composed of L-aspartic, D-alanine and 2,2,4,4-tetramethylthietanyl amine (76). It is approved for use as a sweetener in Australia, New Zealand, Mexico and the People's Republic of China (14), but it is not currently approved for use in Canada or the US. The sweetener is metabolized as a protein, but is 2000-times sweeter by weight than sucrose, adding a negligible caloric value to a food (76). It is reported to have a synergistic sweetening effect when combined with other sweeteners and to leave no aftertaste (14,76). Although its safety in humans has not been confirmed, animal studies have indicated no carcinogenic properties and no reproductive toxicity (14,17,76).

EFFICACY OF INTENSE SWEETENERS IN PEOPLE WITH DIABETES

As the current recommendation in the CDA clinical practice guidelines allows up to 10% of energy to be derived from added sugars (77), intense sweeteners are not a required therapeutic strategy. However, non-nutritive sweeteners and foods sweetened with these compounds have been used by many individuals with diabetes to aid in regulating energy and/or carbohydrate intake and increasing their choice of foods (14).

Effects of individual sweeteners on the management of diabetes

Aspartame

A 24-week, randomized, double-blind, placebo-controlled study of 101 healthy volunteers evaluated the safety of long-term large doses of aspartame. Subjects received 75 mg/kg body weight of aspartame or placebo, incorporated into 3 daily meals, for a 6-month period (equivalent to 10 L of diet soda per day or 1.5-times the ADI). There were no significant differences in plasma glucagon or lipids between the aspartame and placebo treatments (30). The safety and efficacy of aspartame use in individuals with diabetes have also been extensively tested and have consistently indicated that consumption (up to 90 days) of aspartame (even at >3-times the expected daily consumption) does not significantly affect glycemic control (2,77-82), insulin levels (78-80,82,83), blood lipid levels (33,79-82) or blood pressure (BP) (2,30,77-82,84).

Colagiuri and colleagues (82) conducted a 6-week, randomized, double-blind, crossover design study in well-controlled, weight-stable subjects with type 2 diabetes (8 men, 1 woman; BMI=26±2 kg/m^2). The study compared the effect on several metabolic parameters of adding sucrose (45 g/day) or an equivalent sweetening amount of aspartame (162 mg/day) to their usual meals, which were high in complex carbohydrates and fibre. Neither aspartame nor sucrose had statistically or clinically significant effects on glycemic control, lipids, glucose tolerance or insulin action (determined by euglycemic-hyperinsulinemic clamps) in these individuals.

Nehrling and colleagues (83) conducted a larger, 18-week, randomized, double-blind study in subjects with either type 1 or type 2 diabetes (n=62) and compared the effect of aspartame consumption (2.7 g/day) with that of a placebo on glycemic control. They concluded that daily consumption of aspartame did not affect fasting plasma glucose (FPG), 2-hour postprandial BG or glycated hemoglobin levels (A1C) (83). In an open, randomized, crossover design study, Horwitz and colleagues (78) investigated a 3-hour response to a single dose of aspartame (400 mg in a beverage) equal to the

amount found in 1L of sugar-free soda, in nondiabetic women (n=12), and men (n=10) and women (n=10) with type 2 diabetes. All subjects were between 18 and 65 years of age. There was no significant difference between aspartame and placebo consumption on PG, insulin and glucagon concentrations. Gupta and colleagues (85) conducted a study in individuals with diabetes with chronic renal failure (n=23) to assess the effect on plasma amino acid profiles of consuming 10 mg/kg/day of aspartame (the equivalent of 25 packets of Equal®) in a 300-mL glass of milk. The dose used significantly increased plasma concentrations of phenylalanine and tyrosine compared with a placebo, but to values remaining within the normal postprandial range for healthy subjects.

Conclusion: **Daily consumption of aspartame below ADI levels had no significant effect on glycemic control (78,83) or blood lipids (79,82) in persons with diabetes.**

Sucralose

Few studies have assessed the effect of sucralose on diabetes management. A randomized, double-blind, crossover study in subjects with type 1 (n=13) and type 2 (n=13) diabetes compared the effect on short-term glucose response of a single high dose of sucralose (1000 mg) to that of a placebo (cellulose) added to a 360-kcal liquid breakfast (86). Postprandial glycemia did not differ significantly between sucralose and placebo consumption (86).

Conclusion: **Daily consumption of sucralose below the ADI levels had no significant effect on BG concentrations (86).**

Saccharin

Although studies evaluating the use of saccharin by people with diabetes date back to the 1920s (47), few studies have been conducted recently. The most recently published studies have evaluated response to saccharin consumption either in a single dose (78) or daily for a period of time (87) and have not produced a significant effect on PG, insulin or lipid concentrations in persons with diabetes. In 1998, Cooper and colleagues (87) conducted a randomized, crossover study in individuals with type 2 diabetes (n=17), in which their usual diet was supplemented daily with 28 g of sucrose or 30 g of starch with added saccharin for equivalent sweetness for 6-week periods. No significant difference in fasting blood glucose (FBG), plasma insulin, serum TG and urinary excretion of glucose, sodium or potassium was seen with the consumption of saccharin. In 1988, Horwitz and colleagues (78) found no difference in the plasma insulin, glucose or glucagon response of subjects with diabetes (n=10) who consumed either a single dose of 135 mg of saccharin, aspartame or placebo.

Conclusion: **Daily consumption of saccharin, below ADI levels, had no significant effect on BG concentrations or blood lipids in people with diabetes (87).**

Cyclamate

There are few recent studies investigating the use of cyclamate as a sweetener by people with diabetes. Concern has been raised regarding the potential for cyclamates to be metabolized to cyclohexylamine, which can act indirectly as a sympathomimetic amine, thereby influencing BP regulation. However, in a study of 194 patients with diabetes, supplementation with calcium cyclamate (1 g/day as cyclamic acid equivalents) for a period of 7 days did not affect BP or heart rate, even in individuals identified as having a high-metabolizing ability (57). A 4-week, randomized, crossover study compared the effects of sucrose (24 g/day) versus sodium cyclamate (approximately 348 mg/day) in 10 subjects with well-controlled type 1 diabetes (88). Consuming cyclamates did not significantly modify FBG, plasma insulin levels, A1C, blood lipids and body weight.

Conclusion: **Daily consumption of cyclamate below the ADI levels had no significant effect on BG concentrations (88) or blood lipids (88) in people with diabetes.**

D-tagatose

A large oral dose of D-tagatose (75 g) did not significantly alter plasma insulin or glucose levels in subjects with or without type 2 diabetes (n=16, 8 per group). However, oral loading with the same dose 30 minutes prior to a 75-g oral glucose tolerance test significantly blunted the rise in glucose levels observed in the subjects with diabetes (89), suggesting that this sweetener may attenuate glucose disposal by acting on GI factors that potentiate insulin action or inhibit glucagon action or by stimulating a greater insulin response at the time of the test (90). A randomized, controlled trial by Saunders and colleagues (62) investigated the effect of repeated oral doses of D-tagatose (75 g/day over 3 meals for 8 weeks) in healthy individuals with or without type 2 diabetes (N=16, 8 per group) on several metabolic parameters. Despite an earlier suggestion of beneficial effects of D-tagatose on glycemic control (89), daily ingestion of D-tagatose did not modify fasting plasma magnesium, phosphorus, cholesterol, TG, A1C, glucose or insulin levels (62).

Conclusions: **Daily consumption D-tagatose had no significant effect on glycemic control (62) in people with diabetes. Consumption of D-tagatose along with sucrose may lower glycemic response to sucrose (62).**

Stevia

Antihyperglycemic and BP-lowering effects of oral consumption of stevioside have been reported in rodent models of type 2 diabetes (91). Mechanistic studies suggested that the lowering of BP may be the result of an effect on renal calcium balance (92,93) and stimulation of insulin secretion by the beta cells (94). These findings from animal studies have not yet been tested in people with diabetes and therefore cannot be used to make dietary recommendations. However,

there is 1 report from China of results obtained from a multicentre, randomized, double-blind, placebo-controlled study of hypertensive nondiabetic subjects aged 28 to 75 years, with diastolic BP between 95 and 110 mm Hg (95). Each subject was given a 250-g capsule containing stevioside (n=60) or placebo (n=46) 3-times daily and followed at monthly intervals for 1 year. After 3 months, the systolic and diastolic BP in the stevioside group decreased significantly ($p<0.05$) from baseline (systolic: 166.0±9.4 to 152.6±6.8 mm Hg; diastolic: 104.7±5.2 to 90.3±3.6 mm Hg), and the effect persisted throughout the year. Blood biochemistry parameters including lipid and glucose levels showed no significant changes. No significant adverse effects were observed and quality of life assessment showed no deterioration (95).

Conclusions: **There is insufficient evidence to evaluate the potential efficacy of the herb form of stevia/stevioside in the diet of persons with diabetes. Consumption of stevioside may be beneficial to persons with hypertension (95), but the benefits to those with diabetes remain to be determined.**

INTENSE SWEETENERS AND WEIGHT MANAGEMENT

The growing epidemic of obesity in North America (96,97) does little to support the efficacy of intense sweeteners in the war against obesity. Interestingly, a survey by Richardson (98) found that businessmen who restricted sugar intake for weight reduction did not use more intense sweeteners than those who did not restrict sugar intake. Consistent with this, college students were reported to use foods that contained intense sweeteners in addition to the added sugars in their diet (99). It has been hypothesized that if consumers replaced sugar in their diet with intense sweeteners, the proportion of calories derived from carbohydrates would be reduced, while that from fat would increase (100). If this occurred, intense sweeteners could contribute to weight gain rather than weight loss (101).

The relationship between intense sweeteners and appetite, hunger and food intake

The majority of studies aimed at determining the influence of intense sweetener consumption on appetite, hunger and food intake have been conducted using aspartame and are of short-term duration. Canty and Chan (102) randomly assigned 20 healthy, normal weight adults to receive 200 mL of water or a sweetened beverage containing aspartame, saccharin or sucrose 3 hours following breakfast. Hunger ratings, performed every 15 minutes using a self-administered questionnaire, were highest after water, lower with the noncaloric sweetener and lowest with the sucrose-sweetened beverage. Contrary to an earlier study (103) suggesting that sweeteners had an appetite-stimulating effect, the results of this study indicated that noncaloric sweeteners did not increase hunger ratings or food intake beyond that of water (102). Similar conclusions were drawn from a crossover study in obese (n=12) and lean (n=12) non-dieting, healthy women (104,105). The authors examined the effects on hunger ratings, taste preferences and energy intake of 4 breakfast preloads composed of creamy white cheese that differed in energy content (300 or 700 kcal) and was either unsweetened or sweetened with sucrose, aspartame, or aspartame and maltodextrin. Hunger ratings and subsequent energy intake at later meals and snacks were affected by the energy content of the preload breakfast, but not by the type of sweetener (104,105).

The effects of aspartame on food intake were also addressed in a study of normal-weight, healthy young men (n=18) (106). Subjects were randomized to consume, 1 hour before lunch, 1 of the 5 following beverages: 560 mL of aspartame-sweetened drink; 280 mL of mineral water plus 340 mL aspartame-sweetened drink; 280 mL of mineral water with 340 mg encapsulated aspartame; 560 mL of mineral water; or 280 mL of mineral water. Hunger and food appeal were assessed at various time points and food intake measured at a subsequent buffet lunch. Neither energy intake nor macronutrient selection were affected by treatment, but consuming 560 mL of either mineral water or aspartame-sweetened drink suppressed appetite ratings, compared with 280 mL of mineral water.

Another clinical trial, undertaken in healthy lean men (n=11), reported that consuming 375 mL of either sugar-rich soda, intense sweetener-containing soda or mineral water did not affect the energy intake at a later snack and lunch (107). Similarly, in a group of normal-weight, non-dieting men and women, preloads of sugar- or aspartame-sweetened snacks were associated with comparable subsequent food intake, hunger sensations or desire to eat (108). These findings indicated that intense sweeteners, when replacing sucrose, reduced sucrose-derived energy while maintaining food volume, thereby aiding in weight loss. Indeed, in 6 normal-weight men, replacement of sucrose-containing foods by aspartame to covertly reduce their caloric content by 25% was associated with a 10% decrease in total daily energy intake with time (with a trend towards weight loss), since although these subjects increased intake of other foods, it compensated for only 40% of the missing calories (109).

In contrast, 6 men living in a laboratory for 14 days who had one-third of the food items presented to them manipulated to be covertly reduced in calories, increased their intake of other foods sufficiently to compensate completely for the calorie-reduced foods. However, when the regular, calorie-dense version of the foods was made available during the last 3 days of the study, the men failed to compensate and did not reduce their total food intake (110). The authors concluded from these observations that the ability to compensate for caloric dilution appears to be greater than that for caloric concentration.

Conclusion: **In individuals without diabetes, the effects of intense sweetener consumption on appetite, hunger and food intake do not differ from those of water (106-108) or on the energy content of a subsequent meal from that of sugar (106).**

The role of intense sweeteners in weight loss

Few studies have examined the long-term effectiveness of artificial sweeteners as an aid to weight reduction. A prospective mortality study of 78,694 women age 50 to 69 years examined the relationship between the consumption of artificial sweeteners and weight change over a 1-year period. This study concluded that users of these sweeteners were significantly more likely than nonusers to gain weight, regardless of initial weight (111). However, it is not clear from this study whether sustained use of artificial sweeteners helped promote weight loss or prevented weight regain (111). In a 3-week study in 30 normal-weight, free-living subjects, Tordoff and Alleva (112) compared the effect on weight of drinking 1150 g/day of soda sweetened with aspartame with that of drinking soda sweetened with high-fructose corn syrup. They found that although caloric intake with aspartame was reported to be lower in all subjects, minimal weight loss (<1 kg) was seen and only in men. In contrast, drinking the high-fructose soda was associated with a significant increase in energy intake and body weight in both sexes. Both types of soda reduced sugar intake from the diet, leading the authors to conclude that drinking large volumes of diet soda may facilitate weight control.

Blackburn and colleagues (113) undertook a randomized, controlled trial in obese women (n=163) to investigate the effect of consuming or abstaining from aspartame-sweetened foods and beverages during a 16-week weight-loss program and a 2-year follow-up maintenance program. After 16 weeks, all subjects had lost 10% of their initial body weight, but more weight was lost in the aspartame group ($p=0.028$). There was a positive correlation between the amount of aspartame consumed and weight reduction ($r=0.32$, $p<0.01$) (112). Post follow-up, weight regain in subjects consuming aspartame was less than in those abstaining from aspartame-containing products (4.6 vs. 9.4% of initial body weight, $p=0.046$). It was concluded that including aspartame can increase adherence to and benefit long-term weight management programs (113).

Kanders and colleagues (114) also studied the effects of aspartame as an adjunct to a 12-week weight loss intervention that consisted of a balanced, energy-deficit diet, behaviour modification and exercise instruction. Obese, nondiabetic individuals (n=59) were randomly assigned to aspartame supplementation or not. Weight loss >10.5 kg was observed in both groups of men, while weight loss was greater in the aspartame-supplemented women (7.5 vs. 5.8 kg). Adding aspartame to a multidisciplinary weight loss program did not adversely affect weight loss and increased variety and palatability of the diet.

Raben and colleagues (115) compared in 41 overweight people (BMI=28 kg/m^2), the effect on weight and total food intake of a 10-week supplementation with drinks and foods containing either 28% of energy derived from sucrose (152 g/day) or a mixture of artificial sweeteners (aspartame, acesulfame-K, cyclamate and saccharin). Consuming large amounts of sucrose (mostly as beverages) was associated with an increase in dietary carbohydrate contribution (from 49 to 57% of energy), body weight (1.6 ± 0.4 kg) and BP (systolic: 3.8 ± 2.0 mm Hg; diastolic: 4.1 ± 1.7 mm Hg). These subjects partly compensated for the supplemented sucrose by decreasing their intake of unsupplemented foods by 452 kcal/day. In contrast, supplementation with non-nutritive sweeteners was associated with a decrease in weight of 1.0 kg and in systolic and diastolic BP of 3.1 and 1.2 mm Hg, respectively. These results provide evidence that consuming sucrose in large amounts and mostly as beverages can result in overconsumption of calories and weight gain in the short term. In contrast, supplementation with artificial sweeteners is associated with less energy intake and some weight loss. These data indicate that displacing beverages with sucrose with beverages with artificial sweeteners may prevent weight gain.

Conclusions: **Intense sweeteners may contribute to weight management in obesity (88,113,114) and possibly in people with diabetes. The use of aspartame-containing food products may improve weight loss and weight control in a multidisciplinary program (111). People who wish to lose weight may safely use non-nutritive sweeteners, ensuring they are replacing energy-dense foods or sucrose-sweetened beverages (115), not nutrient-dense foods such as milk and fruit juices.**

EFFICACY AND SAFETY IN CHILDREN AND ADOLESCENTS

The American Dietetic Association recommends that non-nutritive sweeteners not be used in children <2 years of age, as the safety of these sweeteners has not been sufficiently assessed in this age group (14,116). There are no data available to provide estimates of the intake of intense sweeteners in children and adolescents in Canada. In the Swedish study (5), diet soft drinks and cyclamate-based table-top sweeteners were the major sources of intense sweeteners. The authors expressed concern that the intake of cyclamates by children could exceed the ADI. Unlike the Swedish study, the French survey, using a 5-day questionnaire designed to estimate a theoretical maximum daily intake of intense sweeteners in children with type 1 diabetes, concluded that it was unlikely that maximum consumption of aspartame, saccharin and acesulfame-K by children exceeded the ADI (3).

Two studies (<13 weeks in duration) of aspartame consumption by healthy children (>2 years of age) and adolescents did not identify safety issues (liver and renal function, hematologic status and plasma levels of phenylalanine and

tyrosine) (14,117). Other studies of aspartame use in children have focused on potential effects on behaviour and cognitive function. In a randomized, double-blind, placebo-controlled crossover study, daily intakes of 34 mg/kg body weight of aspartame had no effect on behaviour and cognitive function in children with (27) or without (118) attention deficit disorder. Children aged 4 to 5 years (N=24) were given 205-mL preload drinks containing sucrose (90 kcal), aspartame, aspartame plus maltodextrin (65 kcal) or water as control. Ad libitum consumption of a variety of foods was measured at 30 and 60 minutes post-preload. All drinks suppressed food intake compared with water, aspartame suppressed food intake less than sucrose (119). Studies in older children examining the other high-intensity sweeteners available in Canada were not found.

Conclusions: **Current surveys in Europe indicate that it is unlikely for intake of intense sweeteners in older children and adolescents to exceed ADI levels (3,5). Aspartame consumption below ADI levels had no effect on behaviour and cognitive function in children (28,118).**

Safety of intense sweeteners during pregnancy

For ethical reasons, metabolic studies determining limits on consumption of intense sweeteners during pregnancy and lactation have been conducted only in animal models (120). Rodent studies have shown that saccharin can cross the placenta and can, due to slow fetal metabolism, remain in the fetal tissues longer than in those of adults, and that this appears to be related to both the dose and duration of consumption (120). Based on the available evidence in animals and lack of contradictory studies in humans, Health Canada does not recommend saccharin for use during preconception and periconception periods.

A number of reviews of aspartame consumption during pregnancy have concluded that there are no epidemiological or experimental data to indicate that aspartame crosses the placenta or that maternal consumption produces any adverse effects to either the mother or fetus (120,121). Intakes above ADI (up to 200 mg/kg) have not been associated with health risks to the fetus (121). Although there have not been studies on the safety of consuming aspartame, acesulfame-K or sucralose during pregnancy, the lack of adverse reports suggests that they are safe. Additionally, a case-control study did not find an association between maternal or childhood aspartame consumption and childhood brain tumours (25). One study in 6 healthy lactating women examined the effects of consuming 50 mg/kg body weight of aspartame on plasma amino acid levels and breast milk consumption (122). No differences were seen in plasma levels. Slight increases in aspartate levels (2.3 to 4.3 µmol/dL) were considered to have little impact on total amino acid intake by the infant (122) and to be safe for lactating women (1,122).

Conclusions: **Due to lack of evidence to support its safety, saccharin is not recommended during preconception and pregnancy. Consumption of aspartame, acesulfame-K and sucralose below the ADI levels has not been shown to be unsafe. However, as pregnancy is not a period for dieting, their consumption should not be used to replace energy- and nutrient-dense foods.**

CONCLUSIONS

Table 4 summarizes the evidence-based conclusions drawn from this technical review. Current CDA nutritional guidelines

Table 4. Summary of evidence for non-nutritive intense sweetener use in diabetes management

- As the current CDA clinical practice guidelines allow up to 10% of energy to be derived from added sugars, the use of intense sweeteners is not a required therapeutic strategy.
- Non-nutritive sweeteners do not stimulate appetite or affect mechanisms that regulate hunger and satiety (*Grade C, Level 3 [106-108]*).
- Use of intense sweeteners as an adjunct to multidisciplinary programs may improve weight loss and management in obesity (*Grade B, Level 2 [113,114]*).
- Intense sweeteners are most beneficial when used to replace energy-dense and nutrient-diluted foods including sucrose, and least beneficial when used to displace nutrient-dense foods such as milk, fruits and fruit juices (*Grade D, Consensus*).
- Daily consumption up to the ADI levels of:
  - Aspartame did not significantly affect BG or blood lipid concentrations (*Grade B, Level 2*).
  - Sucralose did not affect postprandial glycemia (*Grade B, Level 2 [86]*).
  - Saccharin did not significantly affect BG or blood lipid concentrations (*Grade B, Level 2 [87]*).
  - Cyclamate did not significantly affect glycemic control (*Grade C, Level 3 [87]*) or blood lipid concentrations (*Grade C, Level 3 [88]*).
  - D-tagatose did not significantly affect glycemic control (*Grade B, Level 2 [62]*). Consumption of D-tagatose, along with sucrose, may lower the glucose response to sucrose (*Grade D, Level 4 [62]*).
  - Stevioside may be beneficial to people with hypertension (*Grade B, Level 2 [95]*), but the benefits to those with diabetes remain to be determined.
- It is unlikely for intake of intense sweeteners in older children and adolescents to exceed ADI levels (*Grade B, Level 2 [3,5]*).
- Aspartame consumption below ADI levels has no effect on behaviour in children (*Grade B, Level 2 [28,118]*).
- Consumption of saccharin and cyclamates are not recommended during pregnancy (*Grade D, Consensus*). Other intense sweeteners have not been shown to be unsafe if consumed in moderation during pregnancy (*Grade D, Consensus*).

ADI = acceptable daily intake
BG = blood glucose
CDA = Canadian Diabetes Association

include an allowance of up to 10% of total energy intake to be derived from added sugars, but people with diabetes may still choose to use sugar substitutes for the following reasons: to displace sugar and reduce the energy content of their diet; to promote increased fluid intake; to replace sugar in foods that may promote dental caries; to facilitate the use of additional carbohydrate choices in their meal plan for nutrient-dense foods such as fruit and high-fibre breads and cereals.

Longer-term studies in persons with diabetes are needed for the entire group of high-intensity sweeteners. Short-term consumption of aspartame (78,83), sucralose (86), cyclamate (88), saccharin (87) below or at the ADI levels did not alter glycemic control in individuals with diabetes. Short-term consumption of aspartame (79,82), sucralose, cyclamate (57), saccharin (87) did not modify plasma lipids in individuals with diabetes. Daily consumption of D-tagatose had no significant effect on glycemic control (62), and its consumption with sucrose may lower the BG response to sucrose (62) in persons with diabetes. While there is no evidence that acesulfame potassium, often combined with other intense sweeteners, is unsafe (36), there is insufficient evidence to evaluate the safety and claims of metabolic benefits of stevia in persons with diabetes. Consumption of extracted stevioside (not approved in Canada) may be beneficial to non-diabetic individuals with hypertension (95), but the benefits to those with diabetes and the caution for use in individuals who are hypotensive remain to be determined. Intensive sweeteners may be regarded as a support in weight control and in the pursuit of an improved lifestyle that includes regular physical activity and a balanced diet that favours vegetables, fruits, and low-fat and high-fibre foods. Due to the limited number of studies in children and adolescents, evidence-based conclusions cannot be drawn at this time.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the help of Lara Cato in researching the material for this article, the National Nutrition Committee of the CDA in reviewing the material and the evidence-based conclusions prior to submission for publication, and Josie Plescia for her secretarial expertise.

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