POLICY STATEMENT Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

American Academy of Pediatrics

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The Use of Nonnutritive Sweeteners in Children

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The prevalence of nonnutritive sweeteners (NNSs) in the food supply has increased over time. Not only are more children and adolescents consuming NNSs, but they are also consuming a larger quantity of NNSs in the absence of strong scientific evidence to refute or support the safety of these agents. This policy statement from the American Academy of Pediatrics is intended to provide the pediatric provider with a review of (1) previous steps taken for approved use of NNSs, (2) existing data regarding the safety of NNS use in the general pediatric population, (3) what is known regarding the potential benefits and/or adverse effects of NNS use in children and adolescents, (4) identified gaps in existing knowledge and potential areas of future research, and (5) suggested talking points that pediatricians may use when discussing NNS use with families

INTRODUCTION

Nonnutritive sweeteners (NNSs), also known as noncaloric artificial sweeteners or high-intensity sweeteners, were first introduced into the food supply in the late 1800s (eg, saccharin) and were first approved for use as a food additive under the Food Additives Amendment of the Federal Food, Drug, and Cosmetic Act of 1958.[1,2] NNSs increase the palatability of food and beverages without increasing caloric content. It has been proposed that the lack of caloric content of the sweeteners may contribute to weight loss. To date, however, there has been no consistent or conclusive evidence that NNS use lends to a reduction in total caloric intake and thereby to weight loss in humans[3–8] or in animal physiology models.[9] Questions regarding the long-term safety of these agents also remain.[3] Most NNSs, including saccharin, aspartame, acesulfame potassium, sucralose, and neotame, have been approved by the US Food and Drug Administration (FDA) for use as food additives and, as such, have undergone premarket review and approval (https://www.fda.gov/food/food-ingredients-packaging/overview-food-ingredients-additives-colors). Other agents such as stevia and luo han guo have been approved

abstract

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Dr Baker-Smith is the primary author and drafted this policy statement, conducted the literature search and literature review, created the evidence table used to support the content of this policy statement, and assisted with final revisions and review of the document; Dr de Ferranti reviewed the literature, assisted with the drafting and editing of the policy statement, and conducted final revisions and review; Dr Cochran assisted with literature review, contributed to the creation of the evidence table used to support the content of this policy statement, and assisted with the final review of the document; and all authors approved the final version of the manuscript as submitted.

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by the FDA under the "generally recognized as safe" (GRAS) distinction, a distinction that has been determined to be insufficient for ensuring the safety of food additives without specific protections against conflict of interest and without mechanisms to ensure ongoing acquisition of safety data.[10,11]

Concerns regarding the safety of NNSs were initially related to their potential carcinogenic effects. Cyclamate, first approved for use in 1958, was later removed from the list of approved food additives in 1969 because of concerns regarding an association between cyclamate use and the development of bladder cancer.[1,2,10,12] The relationship between cyclamate and cancer was later refuted on the basis of additional scientific data in rats, mice, dogs, hamsters, and monkeys.

Cyclamate was not the only NNS initially suspected of an associated cancer risk. Beginning in the 1970s and 1980s, animal studies suggested an association between saccharin intake and the development of bladder cancer in rodents.[3,13,14] This association was later refuted because it was determined that the "cancer-causing mechanisms in rodents are not applicable to humans."[3,14] Furthermore, human studies evaluating the relationship between saccharin intake and stomach, pancreatic, and endometrial cancer have not identified a relationship between the consumption of saccharin and cancer.[2,3,15,16] Overall, it appears that science does not support a potential carcinogenic effect of cyclamate, saccharin, or sucralose in humans.[3,17–19] The relationship between aspartame and the development of attention-deficit disorders, birth defects, diabetes, and lupus has also been refuted.[3]

A number of health organizations have supported the use of NNSs but within an acceptable dietary intake (ADI) level.[20–25] Despite this, studies conclusively demonstrating the long-term safety and efficacy of NNS agents are lacking.[3,26] Also lacking is published evidence of parental confidence in the safety of NNSs. Despite FDA assurances, published data reveal that parents continue to have questions about the safety of NNSs. For instance, in a single-site study, only 16% of parents responded in the affirmative to the statement, "Nonnutritive sweeteners (ie, Splenda, Sweet'N Low, and Equal) are safe for my child to use."[27] Knowledge of how to identify products containing NNSs remains poor because only 23% of parents were able to correctly identify food products that contain NNSs. In fact, 53% of parents stated they seek items labeled "reduced sugar," but most did not recognize that the sweet taste was instead being provided by an NNS,[27] and only one-quarter of youth were able to distinguish the taste of NNS from sucrose.[28]

Estimating total content of NNS in manufactured products has been challenging. Manufactured products containing NNSs are not required to specify the content of NNS in a product. However, the consumption of NNSs among children has increased.[29,30] The long-term safety or potential benefit of the growing prevalence of NNS use in children has not been systematically reviewed.[31] One barrier to better understanding the health effects of NNS is the difficulty inherent in measuring the amount of NNS consumed at the individual and population levels. The FDA designation of a food item as an additive or GRAS means that although manufacturers must report that a particular product contains a sweetener, there is no obligation to state the amount of sweetener a product contains,[1] making it difficult to estimate how much NNS the average American consumes per day. This is compounded by the fact that NNS can also be found in our drinking water.[32] Thus, even those who do not believe that they have been exposed to NNSs have detectable levels of NNS in their urine.[32,33]

Estimates of consumption are largely based on dietary recall[12,29,30,34,35]; however, such studies are fraught with inaccuracies and thus may result in underestimates of true intake.[29] Ideally, intake of NNS remains within the ADI level. Studies from the late 1990s and early 2000s, including studies in children, had suggested that intake of intense sweeteners was substantially below the ADI.[34–36] Contemporary data addressing total daily intake of NNS in adults and children are limited. According to select studies, intake of particular NNSs (eg, acesulfame potassium or cyclamate) may exceed the ADI.[37] Historically, carbonated beverages have contributed the greatest milligram dosage to total daily intake of NNS (eg, saccharin).[12,38] However, there is a growing and widening variety of food, drink, and consumer products that contain NNSs (eg, chewing gum, oral rehydration solutions, mouthwash, etc; Table 1).[10] Therefore, estimates of intake would be difficult to capture given current methods of reporting.

Ongoing questions also exist regarding the benefits of NNSs. Added sugars are known to have detrimental effects,[39,40] including an association between sugar intake and increased body mass, dyslipidemia, and blood pressure.[40] Recommendations to promote cardiovascular health in children include limiting the total intake of sugar-sweetened beverages (SSBs) to 4 to 6 oz per day in children 1 to 6 years of age and limiting the total intake of SSBs to 8 to 12 oz per day in children 7 to 18 years of age.[41] NNSs have been considered for use among those aiming to reduce their total SSB intake while still preserving the sweet taste. In particular, NNS use has been proposed among individuals with diabetes and among those aiming to lose or maintain weight.

TABLE 1 Commercial Products Reported to Contain NNS

NNS	No. Products	Product Examples
Saccharin	100	Smucker's Low Sugar Reduced Sugar Sweet Orange Marmalade, Bubble Yum Sugarless chewing gum, diet sodas (Tab), yogurt
Aspartame	2307	Jell-O, diet sodas (Diet Coke, Coke Zero, Diet Dr Pepper, Fresca, Tab), Country Time Sugar Free lemonade
Acesulfame potassium	3882	SlimFast, Werther's Original Sugar Free hard candies, Del Monte Mandarin Oranges No Sugar Added, Pedialyte, diet sodas (Pepsi One, Sprite Zero, Fresca)
Sucralose	5148	Lean Pockets, diet sodas (Diet Mountain Dew)
Neotame	114	Sunny D, protein shakes, chewing gum
Stevia	642	Some Muscle Milk products
Advantame	0	N/A
Luo han guo	98	Some Celestial Seasonings products

Adapted from FoodFacts.com (accessed July 12, 2015); Franz M. Amounts of sweeteners in popular sodas. Available at: https://static.diabetesselfmanagement.com/pdfs/DSM0310_012.pdf. Accessed April 28, 2019; and Food Standards New Zealand Australia. Sweeteners. 2018. Available at: www.foodstandards.gov.au/consumer/additives/Pages/Sweeteners.aspx. Accessed April 28, 2019. N/A, not applicable.

However, concerns have arisen that NNS use in animals may alter gut microbiota in such a way that there is an enhanced risk for glucose intolerance, insulin resistance, diabetes, and increased weight.[42,43]

This report summarizes the available literature regarding NNS use in children and adolescents, including the penetrance of these agents into the pediatric food chain and effects on taste preferences in children. This statement also addresses proposed potential benefits of NNSs in specific pediatric populations (ie, those with obesity, diabetes, etc). Consideration of the strength of the data was also included. Our purpose with this statement is not to provide specific clinical guidance regarding the use of NNSs in children but rather to provide a summary of the existing data. Finally, recommendations are made for future directions in research and policy.

METHODS

A systematic review was beyond the scope of this publication; however, the authors used a common search strategy to identify relevant publications. A literature review was conducted regarding the use and safety of NNSs in the pediatric population (ie, 0–18 years of age) in 2011. The search was updated on October 15, 2014, and then again on May 25, 2018, because of delays in publication related to a lengthy review process. A final selection of references was performed by August 20, 2018, resulting in 40 additional references.

The following search terms were used in PubMed (www.pubmed.gov): "nonnutritive sweetener" or the name of each individual FDA-approved nonnutritive sweetener (ie, "aspartame," "neotame," "saccharin," "sucralose," "advantame," or "acesulfame"). "Stevia" also was included in the search because this agent received the designation of GRAS. The search was limited to studies published within the previous 10 years (before the initial search) in human subjects and written in the English language. Eighty-three studies were identified. Studies that did not pertain to the use, safety, potential benefits, or associated risks of NNS use in children were excluded (n = 31). Studies addressing the use of NNSs in pain control were excluded. The reference lists of selected articles were reviewed, and relevant cited references were also included. Additional searches were performed to fill in identified knowledge gaps (n = 30). Finally, policy statements of other organizations on NNS use, including the Academy of Nutrition and Dietetics (AND),[21–23] American Diabetes Association (ADA),[44] and American Heart Association (AHA),[12] were reviewed (n = 4). It should be stated that the highest-quality evidence is derived from randomized controlled trials (RCTs) within the population of interest. To date, however, few such studies exist (n = 6).[4,45–49]

SWEETENERS AND NNSS

Sweeteners can be classified as sugars (ie, brown sugar, cane sugar, fructose, and high-fructose corn syrup), alcohol sugars (ie, isomalt, maltitol, mannitol, sorbitol, and xylitol), and NNSs (ie, saccharin, aspartame, acesulfame potassium, sucralose, stevia, neotame, and advantame). NNSs are high-intensity sweeteners that provide a sweet taste with little to no glycemic response and few to no calories.[1]

Eight NNSs are currently approved by the FDA,[1] and their levels of sweetness range from 180 to 20 000 times sweeter than sucrose (ie, table sugar). Each NNS possesses varying properties; some are stable when heated. Some are contraindicated for use in particular patient populations, such as aspartame use in people with phenylketonuria (Table 2). Most have been approved for use as a food additive and, as such, have undergone a premarket approval process in accordance with stipulations made by

TABLE 2 FDA-Approved NNSs

Type (Approval Distinction)	Commercial Name	Kcal/g	Sweetness Compared With Sucrose	Introduction and/or FDA Approval	Heating Reduces Sweetness	Contraindication and/or Safety Issues
Saccharin (1,2- benzisothiazolin-3-1, 1,1-dioxide) (food additive)	Sweet'N Low, Sugar Twin, Necta Sweet	0	200–700	Introduced in 1879; FDA approved for use	No	None
Aspartame (N-[l-α- Aspartyl]-L-phe, 1-methyl ester) (food additive)	NutraSweet, Equal, Sugar Twin	4[a]	180	Approved for limited use (ie, tabletop sweetener) by the FDA in 1981 and approved for general use in 1996	Yes	Phenylketonuria; reported cases of thrombocytopenia (78)[50]
Acesulfame potassium and/or acelsulfame potassium (potassium 6–methyl-2,2-dioxo-oxathiazin-4-folate) (food additive)	Sunett, Sweet One	0	300	Discovered 1967; FDA approved limited use 1988 and general use (exceptions: meat and poultry) in 2003	No	Associated with cancer in animals at high dose; no known association in humans
Sucralose (1,6- Dichloro-1, 6-dideoxy-β-D- fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside) (food additive)	Splenda	0	600	Discovered in 1976; FDA approved for limited use in 1998 and for general use in 1999	No	None
Neotame (N-[N-{3,3-dimethylbutyl}-L-α-aspartyl-L-phe 1-methyl ester]) (food additive)	Newtame	0	7000–13 000	FDA approved for general use 2002 (exceptions: meat and poultry)	No	Contains phe and asp and is therefore contraindicated in those with phenylketonuria
Stevia (1,1-dioxo-1,2-benzothiazol-3-1), GRAS	Truvia, Pure Via, Enliten	0	200–400	Accepted as GRAS April 20, 2015	Yes	None
Advantame ([N-{3-(3-hydroxy-4-methoxyphenyl)}-propyl-α-aspartyl]-L-phe 1-methyl ester)	None	3.85	20 000	FDA approved for general use 2014 (exceptions: meat and poultry)	No	Determined to be safe for use in children
Luo han guo fruit extract (GRAS)	Monk Fruit in the Raw, PureLo Lo Han Sweetener	Unknown	600	GRAS January 15, 2010; intended for use as a tabletop sweetener, food ingredient, and additional sweetening agent	Unknown	None

Adapted from AND. Scientific opinion on the safety of advantame for the proposed uses as a food additive. *EFSA J.* 2013;11(7):3301; Fitch C, Keim KS; Academy of Nutrition and Dietetics. Position of the Academy of Nutrition and Dietetics: use of nutritive and nonnutritive sweeteners. *J Acad Nutr Diet.* 2012;112(5):739–758; Renwick AG. Postscript on advantame–a novel high-potency low-calorie sweetener. *Food Chem Toxicol.* 2011;49(suppl 1):S1; Kroger M, Meister K, Kava R. Low-calorie sweeteners and other sugar substitutes: a review of the safety issues. *Compr Rev Food Sci Food Saf.* 2006;5:35–47; and Magnuson BA, Roberts A, Nestmann ER. Critical review of the current literature on the safety of sucralose. *Food Chem Toxicol.* 2017;106(pt A):324–355.

[a] Although aspartame contains 4 kcal/g, little is used, and therefore, it essentially provides no extra calories.[51]

the 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act.

Under the 1958 Food Additive Amendment to the Federal Food, Drug, and Cosmetic Act, only substances with GRAS designation do not require premarket approval. Although the market studies for aspartame, acesulfame potassium, sucralose, advantame (an N-substituted analog of aspartame), saccharin, and neotame are not widely available, these NNSs have been studied for safety.[1] Studies number more than 100 for aspartame, nearly 100 for acesulfame potassium, approximately 110 for neotame (in animals and humans), and 37 for advantame (in animals and humans), the NNS food additive most recently approved by the FDA.[1,52,53] Only 2 approved NNSs, *Stevia rebaudiana* and luo han guo (or monk fruit), have been approved under the GRAS notification process. After the passage of the 1958 Food Additives Amendment, President Nixon ordered an evaluation of GRAS substances, largely in response to concerns raised about some of the substances with GRAS designation, including cyclamate. After this order in the 1970s, the FDA hired the Life Sciences Research Office, which then selected qualified scientists (ie, the Select Committee on GRAS Substances) as consultants to review and evaluate the available information on each of the GRAS substances. The select committee's evaluations were made independently of the FDA or any other governmental or

nongovernmental group. In 1972, a GRAS affirmation process began. The FDA established procedures (21 Code of Federal Regulations 170.35) that it would then use to affirm the GRAS status of substances. The GRAS notification process began in 1997. By the end of 2006, 193 GRAS notices were filed, and the glycoside isolated from the plant *S rebaudiana Bertoni* and luo han guo were accepted as GRAS for use in baked foods and soft drinks.[1,3] Additional information regarding NNSs can be found in previously published review articles.[10,21,22,38,43,51–61]

PENETRANCE OF NNSS INTO THE NORTH AMERICAN DIET: HOW MUCH NNS DO CHILDREN ACTUALLY CONSUME?

Information about NNS consumption by children and adolescents is mostly derived from dietary recall[12,62–69] and cross-sectional analysis,[29,30] which limits the ability to estimate the quantity of NNS consumed because the quantity of NNS per serving of any given food is not publicly available and because dietary recall is prone to error. Early studies found that approximately 15% of the population older than 2 years old consumes some type of NNS per year (eg, 2003–2004).[70] Older review articles concluded that pediatric NNS intake was within the ADI level.[34,62,63] Still others have found, on the basis of estimated intake from 24-hour dietary recall, that intake of cyclamate and saccharin may exceed the ADI for some youth.[69] Regardless, intake of NNS among children tends to exceed NNS intake for adults when assessed as milligrams per kilogram of body weight.[12]

The prevalence of NNS use is increasing, and inclusion of NNSs in daily food products is more pervasive.[10,70,71] A single prospective study of youth with diabetes mellitus (n = 227) estimated, on the basis of a 5-day food diary, that the theoretical maximum daily intake of saccharin, acesulfame potassium, and aspartame did not exceed ADI but varied between 5% and 94% of the ADI.[36] According to Web sites such as FoodFacts.com, the number of foods and consumer products that include at least 1 NNS as an ingredient has tripled within the last 4 to 5 years. In 2010, Yang[72] found that according to FoodFacts.com, 3648 products contained at least 1 NNS.[10] As of July 12, 2015, approximately 12 291 products contained at least 1 NNS.[10]

People are not always aware of their intake of NNS. Some artificial sweeteners can be found in groundwater and drinking water, although at magnitudes below the ADI level.[32] Furthermore, people inadvertently consume NNS, according to a recent study of 18 reported "nonconsumers," 44% of whom had sucralose in their urine that was unexplained by the trivial amounts of sucralose that are sometimes reported in the water supply.[32,33]

The majority of NNS intake is derived from intake of NNS-containing beverages (~11%), followed by food (~4%) and individual NNS packets (~1%).[38] Data from the NHANES 1999–2000 to 2007–2008 show that the percentage of children consuming NNS-containing beverages increased from <1% to >7%.[29] More recent NHANES cross-sectional data analysis (2009–2012) revealed that 25.1% of children, compared with 44% of adults, reported consumption of NNSs.[30] Most reported daily use (80% of children and 56% of adults). Analysis of the 2009–2012 NHANES data suggests that NNS intake is higher in women and girls, individuals with obesity (versus those with overweight or normal weight), non-Hispanic white individuals (versus non-Hispanic African American or Hispanic individuals), and individuals in the highest tertile of income.[30] Between 4% and 18% of carbonated beverages consumed by children contain NNSs.[71] Household purchase of NNS-containing beverages has also increased at the same time that the purchase of SSBs has decreased: between 2003 and 2010.[73]

International recommendations have established an ADI (per kilogram) for NNSs. The ADI is typically 100 times lower than the dose of the sweetener known to cause toxicity in animals.[71] The concept of the ADI was established by an international scientific committee and the Joint Food and Agriculture Organization of the United Nations–World Health Organization Expert Committee on Food Additives. Other organizations have reported ADI levels for various NNSs, including the European Food Safety Authority and the Danish Veterinary and Food Administration (Table 3).[70] US federal regulations (FDA Code 21 Code of Federal Regulations 170) do not require that the amount of NNS in a food item be listed on the product label if it has been determined to be safe for use in a particular food.[1] However, without proper knowledge of true content, it is difficult to know whether intake of a particular sweetener is within the ADI level.

It is also difficult to know whether intake of a particular NNS by a child is within the ADI level, but it is worth noting that there have been few cases of reported adverse events related to NNS intake.[50] Proponents of NNS use argue that safety information can be assumed on the basis of more than 30 years of use of these agents with relatively few reported adverse effects. However, it is also true that there has been no systematic or formal method for capturing and recording adverse effects related to the use of these agents.

Given the proliferation of products containing NNSs in the food supply, which may lead to both increased consumption and combined use of NNSs, there is a need for contemporary peer-reviewed studies

TABLE 3 ADI Level

Sweetener	JECFA ADI, mg/kg	EFSA ADI, mg/kg	DVFA ADI, mg/kg	FDA ADI, mg/kg	Number of Packets Equivalent to ADI (Based on a 68-kg Person)
Saccharin (Sweet'N Low)	5	5	5	15	250
Aspartame (NutraSweet and Equal)	40	40	15	50	165
Acesulfame potassium (Sweet One)	15	9	40	15	165
Sucralose (Splenda)	15	15	15	5	165
Neotame	0–2	1	Unknown	0.3	200
Stevia	4	4	Unknown	12	30
Advantame	0–5	5	4000	33	4000

Adapted from US Food and Drug Administration. Food additives and ingredients. Available at: www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients. Accessed March 26, 2019; Gardner C, Wylie-Rosett J, Gidding SS, et al; American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity and Metabolism, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Disease in the Young, and the American Diabetes Association. Nonnutritive sweeteners: current use and health perspectives: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation*. 2012;126(4):509–519; and Mattes RD, Popkin BM. Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms. *Am J Clin Nutr*. 2009;89(1):1–14. DVFA, Danish Veterinary and Food Administration; EFSA, European Food and Safety Agency; JECFA, Joint Food and Agriculture Organization of the United Nations–World Health Organization Expert Committee on Food Additives.

to estimate the current prevalence of NNS use, amounts consumed by children, and any potential adverse effects.

IMPACT OF NNSS ON APPETITE AND TASTE PREFERENCE

Studies regarding the potential impact of NNS intake on appetite and taste preference can be divided into animal studies and human studies. Animal models have shown that nutritive sweeteners activate the sweet-taste receptors (ie, T1R family and α-gustducin receptors).[74,75] According to animal studies, saccharin intake weakens the ability of Sprague Dawley rats to signal the caloric "postingestive consequences of eating" so that if saccharin is administered, rats did not regulate their intake of sugar-sweetened food and/or beverages after saccharin-sweetened solution intake.[76] This study suggests that NNS intake may affect normal responses to caloric intake such that overeating may be more likely if the diet after NNS administration is a sweeter diet.[76]

In children, the taste receptors are located in the lingual taste buds and along the intestinal mucosa.[77] Activation of the sweet-taste receptors results in stimulus to the pleasure-generating loci of the brain,[77] triggering glucose uptake and appetite regulation. Individuals vary in their ability to perceive taste, and thus, individuals differ in their potential "gain" achieved from various sweet stimuli.[78,79] It was once believed that only nutritive sweeteners activate the sweet-taste receptors; however, it is now known that NNSs, which are several hundred times sweeter than table sugar, also activate these receptors.[70] The effect of NNS activation on taste preference, food intake, the activation of metabolic pathways, and appetite is not well understood.[80,81]

Human studies have been inconsistent in their reporting of the potential impact of NNS use on appetite and taste preferences. Furthermore, genetic differences in taste perception may also exist and influence study results.[82] A small study of 10 healthy adults given 1 of 4 drinks that contained either glucose alone or glucose plus 1 of 3 sweeteners (eg, 45 g glucose and 150 mg aspartame, 45 g glucose and 20 mg saccharin, or 45 g glucose and 85 mg acesulfame potassium in 250 mL of water) did not report differences in hunger or fullness within 60 minutes of ingestion.[83] In contrast, a single study of 115 college students 18 to 22 years of age given either Sprite Zero (NNS-containing beverage), mineral water, or regular Sprite reported that those who consumed NNS (ie, Sprite Zero) were more likely to subsequently choose a bag of chocolate M&M's (43%), whereas those who consumed a nutritive sweetener (eg, regular Sprite) or water were more likely to select a less-sweet snack, such as water or chewing gum (41% and 33%, respectively).[84] The authors concluded that participants who consumed NNSs felt less satisfied with what they had drunk compared with those who consumed a sugar-sweetened or an unsweetened beverage ($P = .004$).[84] As for assessing how intake of NNS influenced preference for sweet food, researchers found in this study of 115 college students that participants who consumed NNS were more likely to provide the names of high-calorie food items compared with those who consumed a sugar-sweetened or an unsweetened drink ($P = .001$)[84] after consumption of the NNS-containing beverage.

NNS use in children may be associated with a greater preference for sweet foods[77]; however, the effect of NNSs on taste preference is not well understood. Humans have an innate preference for sweet foods, and children in particular prefer high levels of sweetness.[77] Children who consume large amounts of SSBs may

tend to prefer foods that are richer in both sugar and calories. The American Academy of Pediatrics (AAP) recognizes the detrimental effect of high sugar content on the health of children and the propensity that high sugar content has for promoting obesity in childhood.[6,39,85–87] The AAP recommends against routine consumption of sports and energy drinks because of their high sugar content.[39] A single, small population study found that adults who consumed NNSs tend to prefer a sweet versus salty and/or savory snack after this ingestion. The authors suggest that NNS intake can increase the motivation for one to access sweet relative to savory snacks[88] and thereby alter energy balance in such a way that children who consume these agents are more likely to consume sugary food and drinks.[84] The temporal correlation between the increase in childhood overweight and obesity and the increase in intake of NNS-containing beverages is suggestive of a relationship.[38] However, the relationship may be one of reverse causality, whereby children who have obesity (or their parents) may be substituting food or beverages sweetened with NNSs for those containing sugar in an attempt to limit caloric intake.

In summary, increasing trends in NNS use are coincident with an increase in the prevalence of childhood obesity. Data suggest but do not conclusively demonstrate that NNS use may promote the intake of sugary food and drink by affecting taste preferences. It has been demonstrated that excessive intake of SSBs (and increased calories) has been associated with childhood obesity. Additional information regarding the effects of NNS use on taste preferences and caloric intake and comparison of the long-term effect of NNS-containing versus SSBs is needed.

SAFETY AND NNS USE

Most NNSs have been approved by the FDA for use as a food additive; 2 NNSs were approved under the GRAS distinction for a particular intended use.[1] Reviews and investigative studies discussing and evaluating the safety of NNSs, including sucralose,[19] have been published. Studies investigating the potential toxic effects of NNSs have been performed in animals[55–58] and humans.[51,59] Results from these more recent studies have concluded that there are no potential teratogenic effects or negative effects of NNS use on weight or development in animals. However, cases of aspartame-induced thrombocytopenia have been reported.[50] Furthermore, aspartame is uniformly contraindicated in people with phenylketonuria.

NNS USE AND CANCER RISK

Concerns regarding a potential relationship between NNSs and cancer were raised shortly after the introduction of NNS into the food supply.[1,10] Cyclamate was first approved for use in humans in the 1950s[89]; however, concerns arose regarding a potential increased risk for bladder cancer after use of cyclamate in rats.[89] It was also proposed that the metabolism of cyclamate to cyclohexylamine, which is toxic to rats and dogs, caused testicular atrophy and impaired spermatogenesis.[89] When administered to nonhuman primates, 3 of 14 monkeys given cyclamate developed neoplasms versus 0 of 16 controls. The 3 tumors, developed after receipt of "the equivalent of ~30 calorie-reduced drinks" (containing cyclamate), were a metastatic adenocarcinoma of the colon, a metastatic hepatocellular carcinoma, and a papillary adenocarcinoma of the prostate. The authors concluded that there was "no evidence for carcinogenicity of sodium cyclamate because the tumors in the treatment group were of different histologies and the tumors occurred at a rate frequently observed in monkeys."[89] To date, there have been no case control studies of cyclamate, particularly related to tumor formation in humans.[89] The relationship between cyclamate and cancer was later refuted, and permissions for use of cyclamate were thus reinstated in 1992.[2]

A study of Sprague Dawley rats fed diets supplemented with 0%, 5%, and 7.5% (of the total diet) saccharin experienced differences in the proliferation of the epithelial cells (used as a marker of cancer risk) by diet and concentration of saccharin.[14] However, this study was not deemed to be relevant to humans because the form of saccharin used, sodium-saccharin, is considered "representative of a large group of sodium salts known to act as tumor promoters in the male rat urinary bladder when high doses (of saccharin) are administered."[14] The FDA reports that a total of 30 human studies have been conducted to date and have not found an association between saccharin use and cancer of any type.[1] A large case control study of people with bladder cancer (n = 3010) and controls (n = 5783) found no association between self-reported past NNS use and bladder cancer.[66] However, not all studies have agreed with this conclusion.[16] A number of observational studies later determined that the relationship between saccharin and bladder cancer was specific to rodents.[17] Saccharin was removed from the list of potential carcinogens in 2001 by the National Toxicology Program of the National Institutes of Health.[10]

A case control study of adults with incident neoplasia (eg, stomach, pancreas, and endometrium) versus unaffected controls did not find greater odds of cancer among those exposed to NNSs.[90] However, 1 of the limitations of this case control study

was low NNS use among participants and potentially insufficient sample size to detect even weak associations between NNS use and cancer.[90]

A systematic review of the safety and potential carcinogenic effect of aspartame in mice found no association between aspartame administration and risk of cancer.[91] A meta-analysis of studies of aspartame in rats showed no association between aspartame and cancer.[92] A review of human (adult) cohort and case control studies showed no relationship between most types of cancer and aspartame use.[18,51,92,93]

Newer data have failed to demonstrate an association between NNS use and cancer.[90] The long latency period, the penetrance of NNSs into the food supply (making it difficult to isolate an adequate unexposed control group), and the diversity of potential mechanisms have made it difficult to definitively exclude potential carcinogenic properties of NNSs but also make it difficult to conclude that there is any such association. The type of research that would more definitively address the effects of NNS intake over the long-term and across the life span (for example, long-term randomized clinical trials or prospective cohorts with well-defined measures of exposure over multiple time points) is not likely to occur.

In summary, observational data in adult-human studies show no association between NNS use and cancer. There are no long-term studies in children. Studies have been limited to animal and adult-human studies, and the long-term risk of cancer and other conditions among children who use NNSs is not known and is likely to be difficult to obtain.

NNS USE IN SELECT PEDIATRIC POPULATIONS

It can be reasonably argued that certain subpopulations of children might benefit from the use of NNSs. For example, children and adolescents who have obesity might benefit from lower total caloric intake. Children who have type 1 or 2 diabetes mellitus might also benefit from the lack of a glycemic response while enjoying the sweet taste of NNSs. Similarly, those with multiple metabolic or cardiovascular disease risk factors also might experience a benefit because excess carbohydrate intake is likely a factor contributing to their health risk.[94–96]

NNS USE AND CHILDREN WITH OBESITY

NNSs pass through the human gastrointestinal tract without being digested, providing sweet taste without added calories, a property that is potentially advantageous for preventing and controlling obesity given the association between sugary beverage consumption and obesity.[6,64,87,97] However, the data are conflicting as to whether consuming NNSs leads to weight loss or weight gain.[6,87]

Swithers et al[98] also provided animal studies reporting that use of artificial sweeteners may increase weight gain. Observational studies in adults show that NNS intake is associated with increased BMI. Analysis of the San Antonio Heart Study, an adult prospective cohort study, showed a dose-response adverse effect of NNS intake on overweight and obesity status over 7 to 8 years of follow-up.[99] However, these data are vulnerable to reverse causality because it has been demonstrated that individuals who are attempting to lose weight are more likely to use NNSs.[26] Additionally, the San Antonio analysis is subject to the same vulnerabilities regarding the accuracy of estimated NNS intake, particularly because the baseline data were collected decades before the current era and estimates were reliant on dietary recall.

Several cross-sectional studies in children and adolescents have also reported positive associations between NNS intake and BMI (ie, high NNS intake is associated with higher BMI).[64,100] However, results from longitudinal follow-up are conflicting, with a few studies supporting these findings[6,86,87] and others suggesting either no relationship[101] or a small beneficial effect of NNS intake on BMI.[97]

A double-blind RCT from the Netherlands found that replacement of SSB intake with NNS intake in school-aged children was associated with reduced weight gain (not weight loss) during an 18-month period.[4] A study of aspartame use in adults with overweight (eg, mean age 19 years) was associated with greater weight reduction than among the control population.[102] Similarly, a study from South Africa found that intake of 25 mg of sucralose per day by youth 6 to 11 years of age was associated with a lower BMI-for-age *z* score (control and nutritive sweetener of 7.1 and micronutrient and NNS of 6 versus control and sucrose of 10.8 and micronutrient and NNS of 10.9) compared with sugar intake. In contrast, a higher weight-for-age *z* score change was associated with NNS use in a separate study.[5] Prospective studies have revealed mixed results: Newby et al[103] did not identify an association between NNS intake and weight change in a prospective cohort study of 2- to 5-year-olds (n = 1345) but reported that intake of diet soda was low (<5 oz per day), with poor correlation seen between estimated beverage intake at the time of the first visit compared with at the second visit. A prospective study investigating the effect of intake of SSBs and NNSs on weight among school-aged youth (n = 164) found that for each 12 oz of diet soda consumed per day, there was a 2-year BMI *z* score that was 0.156 higher than predicted on the basis of baseline-BMI *z* score.[6] A prospective cohort study of 4746 youth found that consumption of low-calorie soft

drinks (positive association; $P = .002$) was associated with weight gain, whereas consumption of white milk (inverse association; $P = .03$) was associated with weight loss.[104] Analysis of the relationship between NNS use and weight gain, however, did not control for parental weight and other important confounders.[104] Limitations of prospective cohort studies include failure to control for other dietary and lifestyle factors[105] and shorter long-term follow-up. Interpretations of the relationship between NNS use and BMI are limited by the inability to determine causality because of cross-sectional study design as well as reverse causality and inaccurate dietary recording in prospective cohort study design.[105] Youth who consume NNSs may have different food consumption patterns and a variety and parental and environmental factors not adjusted for in the prospective studies that may affect the relationship between NNS use and BMI.

Meta-analysis of 15 RCTs examining the relationship between NNS use and BMI in adults and youth (ages 10–65 years) reported that intake of NNS is associated with modestly reduced body weight, BMI, fat mass, and waist circumference (WC) with a mean reduction in weight of 0.8 kg.[105] However, RCTs suggest that substituting NNSs for SSBs is associated with a modest reduction in body weight for youth with the highest baseline BMI but not for all youth. Ebbeling et al reported results from a pilot study for an RCT evaluating the potential impact of replacement of SSBs with NNSs on body weight in youth and found that change in BMI, adjusted for sex and age, was 0.07 ± 0.14 (mean ± SE) for the intervention group and 0.21 ± 0.15 for the control group with a net difference of –0.14 ± 0.21, which was not significant. Baseline BMI was a significant effect modifier such that youth in the upper baseline-BMI tertile experienced a significant reduction in BMI between the intervention (–0.63 ± 0.23) and control (+0.12 ± 0.26) groups.[47] A systematic review and meta-analysis of NNS use and cardiometabolic health evaluating change in BMI among NNS consumers 12 years and older from 7 RCTs and 30 observational studies reported mixed results. Analysis of data from 2 of the 7 selected RCTs found that use of NNS was not associated with a significant effect on BMI over a 6- to 24-month period (–0.37; 95% confidence interval [CI]: −1.10 to 0.36; I^2: 9%).[8] Two cohort studies showed a possible correlation between NNS use and BMI over a 3- to 13-year period, and a third cohort study found that participants who consumed NNSs daily had a greater increase in BMI during an 8-year follow-up period.[8] As highlighted in the systematic review, overall, data suggest an increase in BMI with NNS use over the long-term without confirmation of these findings via RCTs.[8]

Controlled experimental studies have tried to better address the question of the effect of NNS on weight by giving controlled meals and measuring caloric intake after the controlled meals. Some studies show lower calorie consumption after foods containing NNSs compared with calorically sweetened foods,[106] but other studies support the phenomenon of "make-up" calorie consumption, showing higher intake[107–110] immediately after NNS intake. The make-up theory has not been proven conclusively[81] and represents only the immediate postprandial effects of NNS intake.

Most short-term studies support a beneficial role of NNS in weight loss.[111] A patient-blinded prospective cohort study in adults comparing satiety, energy intake, and body weight during a 10-week supplementation with either sucrose or artificial sweetener found a significant but modest reduction in fat mass and body weight with artificial sweetener use.[112] A randomized 25-week intervention study of 103 adolescents 13 to 18 years of age that included home delivery of noncaloric beverages (4 servings per day for the adolescent and 2 servings per day for each additional household member) revealed an additional BMI decrease of 0.08 for every 1 at baseline. This study found that the effect of NNS use on BMI in adolescents was most significant for adolescents with a baseline BMI >30.[10,47] A different RCT in children that combined NNS use with total caloric restriction did not find an association between NNS use and weight loss.[102] Given the multitude of factors affecting weight, including high-fat- and low-water-intake diets and the complex behavioral interactions related to response to use of NNS, some have argued that NNS use alone may not be an effective remedy for weight loss.[113]

The long-term effect of NNS use on weight remains poorly defined, and thus far, data suggest the benefits are limited.[69,114] A prospective double-blind study showed that children 4 to 11 years of age with normal weight who consume a beverage containing NNS per day experience less weight gain over an 18-month period compared with those who consume sugar-containing beverages[4]; the change in weight between the 2 cohorts differed by 2.2 lb (1 kg). The America On the Move study found that, combined with additional changes in lifestyle, use of NNSs may contribute to slowed weight gain in overweight and at-risk children[46] over a 6-month study period. A study in children with obesity showed that use of NNSs contributed to slowed weight gain over the first year, but the difference in weight was not maintained during the subsequent year even when controlling for confounders such as screen time, parental BMI, energy intake, physical

activity, and fat consumption.[45] In that study, Ebbeling et al found that NNS use did not result in a significant change in BMI after 2 years of replacement of SSBs with NNSs. Systematic reviews of the existing data concluded that in children, NNS use may prevent excess weight gain over a period of 6 to 18 months but that, in general, studies evaluating the relationship between NNS intake and obesity are lacking rigor.[26] According to 1 published systematic review, use of NNSs in place of sugar, in children and adults, leads to reduced energy intake and a small reduction in body weight (on average, 1.3 kg).[115] Finally, a Cochrane Review reported that NNS use was associated with a significantly reduced body weight (−1.07 kg [95% CI: 0.41 to 1.72]), and among people younger than18 years, the NNS group demonstrated a significant reduction in body weight (1.18 kg [95% CI: 0.34 to 1.04]), an association that was not demonstrated for adults.[116]

In summary, the preponderance of data suggests that the use of NNSs can lead to weight stabilization or a small degree of weight loss by helping lower total caloric intake, especially among children and adolescents with obesity. Studies suggest that NNSs may be considered part of a comprehensive program and a substitute for foods and beverages containing caloric sweeteners for weight loss or weight maintenance. The current data would suggest that depending on baseline BMI and without easily taking into account what else is being consumed or substituted for, NNS use is associated with a modest improvement in weight. However, the long-term effects of NNS use in children and adolescents, including use pertaining to weight loss or weight management, are currently unknown.[31,106]

NNS USE AND EFFECTS ON METABOLIC SYNDROME AND DIABETES

Observational and experimental data in adults suggest that the use of NNSs may alter glucose metabolism in the presence of obesity, although these studies are subject to the same vulnerabilities as described above with regard to obesity.[8] Cross-sectional analysis of 2856 adults participating in the NHANES demonstrated that aspartame intake affects the association between BMI and glucose tolerance (interaction: $P = .004$), showing worse glucose tolerance with increasing BMI in those reporting consumption of aspartame.[117] Similarly, cross-sectional analysis of the Framingham Offspring Cohort showed an association between diet soda consumption, as assessed by a food frequency questionnaire, and metabolic syndrome.[7]

Prospective cohort data from the Coronary Artery Risk Development in Young Adults (CARDIA) study of the evolution of cardiovascular disease risk showed that among young adult NNS consumers 18 to 45 years of age, consumers of NNS were more likely to have metabolic syndrome and a higher WC. In comparing those who consumed a Western diet and NNSs versus individuals who consumed a Western diet but not NNSs, there was no significant difference in WC, the presence of high fasting glucose, low low-density lipoprotein concentration, high triglycerides, high blood pressure, or overall metabolic syndrome. However, young adults who consumed a prudent diet and NNSs (prudent consumers) were less likely to have a high fasting glucose (hazard ratio [HR]: 0.75; 95% CI: 0.57 to 0.99) and a low high-density lipoprotein concentration (HR: 0.69; 95% CI: 0.54 to 0.87). There was no significant difference in the presence of metabolic syndrome among consumers of the Western diet and prudent diet consumers of NNSs. However, prudent diet nonconsumers of NNSs were less likely to have metabolic syndrome (HR: 0.64; 95% CI: 0.5 to 82) compared with consumers of a Western diet. Results from this study suggest that a prudent dietary pattern is consistently associated with lower risk for metabolic syndrome, but being a nonconsumer of NNSs is not.[118] Use of NNSs can be associated with a lower likelihood of high fasting glucose and of low high-density lipoprotein but did not significantly affect WC (prudent nonconsumers were actually less likely to have a high WC [HR: 0.78; 95% CI: 0.62 to 0.97]), the likelihood of high triglycerides, or metabolic syndrome.[7,118] Findings from the CARDIA study were also observed in other prospective cohorts. A prospective analysis of the association between beverage consumption (SSBs and NNS soda intake) found that intake of greater than or equal to 1 soft drink per day (regular or diet) was associated with a higher prevalence of metabolic syndrome.[7] Again, given the cross-sectional and observational design of these studies, causality cannot be determined; nonetheless, data suggest that there is a correlation between NNS use and metabolic syndrome.

The Multi-Ethnic Study of Atherosclerosis cohort study showed that daily consumption of diet soda was associated with a 36% higher relative risk of metabolic syndrome and a 67% higher relative risk of type 2 diabetes mellitus.[68] However, once adjustments were made to account for baseline measures of adiposity, the association between diet soda consumption and metabolic syndrome was no longer significant, but the association between diet soda consumption and diabetes remained.[119] Findings suggest that additional factors among those who consume diet sodas may be associated with a greater risk for diabetes mellitus and metabolic

syndrome. Analysis of the Framingham study stopped short of reporting an association between NNSs and WC but did find that prudent nonconsumers of NNSs were less likely to have a higher WC.

In the Atherosclerosis Risk in Communities Study, diet soda consumption was associated with incident metabolic syndrome ($P <$ .001 for trend).[120] Again, causality cannot be determined in observational study designs, and there are likely significant confounding factors, but longitudinal cohort studies show that there is an association between NNS use and abnormal glucose metabolism in adults.[7,118–120]

Few data exist regarding the role of NNSs in children and youth with diabetes, insulin resistance, or metabolic syndrome. One small study of youth and young adults 12 to 25 years of age with type 1 (n = 9) and type 2 (n = 10) diabetes mellitus compared the effect of drinking carbonated water versus carbonated beverages with NNSs on glucose tolerance (with a 75 g oral glucose tolerance test) using a crossover design.[121] According to this study, there were no differences in glucose or C-peptide secretion in people with either type 1 or type 2 diabetes mellitus after NNS consumption. Youth with type 1 diabetes mellitus released more glucagonlike peptide 1 after they consumed NNS-containing carbonated beverages versus carbonated water; no differences were seen in youth with type 2 diabetes mellitus.

A systematic review of the evidence from prospective studies evaluating the association between early life NNS exposure on long-term metabolic health identified conflicting results from 2 RCTs and 6 prospective cohort studies.[122] Studies selected included a total of more than 15 000 children exposed to NNS for >6 months.[122] The Growing Up Today Study, a prospective cohort study that relied on questionnaires administered between 1996 and 1998 to examine the relationship between beverage intake and change in BMI among >10 000 boys and girls ages 9 to 17 years, demonstrated a relationship between diet soda consumption and increased BMI over 2 years' follow-up in boys (P = .016) but not girls (P = .152).[87,122] Data from the Framingham Children's Study[46,122] among 3- to 15-year-olds revealed that although there was no consistent trend in body fat associated with intake of SSBs or NNS-containing beverages, the highest NNS intake was associated with increased body fat, as measured by skinfolds.[111]

The mechanism by which NNSs might adversely affect body weight, insulin resistance, and long-term metabolic risk is unknown, but 1 hypothesis is that it results in adverse effects on the gut microbiome. Alterations in microbiota structure and function have been associated with a greater propensity for developing metabolic syndrome.[123] Suez et al[42] published a small but frequently cited study in rodents with some human data comparing the effects of NNSs (eg, saccharin, sucralose, and aspartame) on glucose tolerance in mice and changes in the intestinal microbiota.[43] The animal data showed that NNS intake, particularly saccharin, leads to a change in the structure and function of the microbiota. A small study in human volunteers (who did not previously consume NNSs) showed that receipt of saccharin within ADI levels for 5 days was associated with the development of glucose intolerance.[42] The findings from these animal data and the small, single, human (adult) study suggest a detrimental effect of NNS use on gut metabolism, whereas a systematic review suggests that NNS use does not alter blood glucose levels over time.[124] In adults, observational data from the CARDIA study show that adults who consume diet soda beverages at baseline, regardless of whether they followed a "prudent" (eg, fruit, fish, and whole grains) or Western dietary pattern (eg, fast foods, refined grains, and sugar-sweetened soda), had higher rates of metabolic syndrome compared with those who did not consume diet soda beverages.[94,118]

Better understanding is needed concerning the effects of NNSs on metabolism and risk of diabetes,[125] including whether NNS intake is merely correlated with a higher risk of metabolic syndrome and diabetes or there is a causal and harmful relationship mediated through the gut microbiome or other as-yet-unidentified pathways.

NNS USE AND CARDIOVASCULAR DISEASE RISK FACTORS

Greater sweetened beverage use has been associated with increase obesity, increased central obesity, and abnormal perturbations in the lipid profile, all of which are risk factors for premature cardiovascular disease.[40] Although consumption of added sugars is known to cause detrimental effects on lipid concentrations,[94,96] no clinical trials have addressed the effects of NNSs on lipid concentrations in childhood.

Current data regarding the potential benefit of NNSs in modifying cardiovascular disease risk factors are limited but suggest an association between NNS consumption and metabolic syndrome, an association that may be limited by reverse causation. There are no conclusive data regarding the risk of cardiovascular disease events and NNS intake.

NNS USE AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM

The lay press has raised the concern that NNS use is associated with behavior, cognition, hyperactivity, and attention issues. Two RCTs show no

relationship between NNS use and behavior and cognition among school-aged children.[48,126] Several review articles regarding the potential impact of NNS use on behavior have been published.[114,127,128] Some data in adults also suggest an association between short-term aspartame consumption and more irritable mood, depression, and poorer performance in spatial orientation.[129] To date, however, there have been no studies to conclude that there is an association between attention-deficit/hyperactivity disorder (ADHD) and NNS use.[128] No literature was found to support a relationship between NNS use and autism.[130]

At the present time, there are no data to support an association between NNS use and the development of ADHD or autism in children or worsening of ADHD symptoms.[48]

OTHER POTENTIAL HEALTH EFFECTS

With the exception of the use of aspartame and neotame in children with phenylketonuria, there are no absolute contraindications to NNS use in children. NNSs may help to reduce the incidence of dental caries in children.[131]

PUBLISHED GUIDANCE AND RECOMMENDATIONS

Several organizations have published summary statements regarding the use of NNSs, including the AND, ADA, and AHA.[21–23,41] The AND states that "consumers can safely enjoy a range of nutritive and nonnutritive sweeteners when consumed in a diet that is guided by current federal nutrition recommendations, such as the *Dietary Guidelines for Americans and the Dietary References Intakes*."[21,22] With regard to the potential benefit of NNSs on weight loss, the AND states that there is a good level of evidence to conclude that NNS use, as part of a comprehensive weight loss or maintenance program, may be associated with weight loss and lead to improved weight management over time in adults; the statements for children were less definitive because of a lack of data. Information regarding use, safety, effect on taste preferences, and potential benefits in special populations was either limited or not available for other NNSs.

The ADA and AHA published a joint summary statement on NNSs in 2012 supporting the position that NNSs are safe when consumed within the ADI levels established by the FDA. Furthermore, the ADA and AHA have argued that NNSs may be helpful in reducing weight gain by limiting caloric intake if used in such a way that total diet caloric intake is reduced. The statement specifically did not address NNS use in children.[38]

RESEARCH GAPS

Gaps remain regarding our knowledge of the impact on NNS use on energy sensing and effects on glycemic control, appetite, and dietary intake for >6 months, and even fewer data exist specifically addressing the pediatric population.[132] Future research should explore novel approaches to assessing the long-term effects of NNS use in children (both type and amount), the effect of age of exposure to NNSs and the development of taste preferences, and the effects of age of exposure to NNSs on the development of diabetes mellitus, obesity, early cardiovascular disease, and the developing brain. Research should explore these topics across the age continuum: toddlers, children, and adolescents. Comparisons should be made with nutritive sweeteners and other beverages (eg, water and milk). Additional research is needed regarding genetic differences that may affect a child's response to a particular NNS and to determine if various NNSs differ in their benefits or risks. Approaches should take into consideration the need for long-term follow-up, adjust for multiple exposures, and account for imprecise exposure measures.

SUMMARY AND RECOMMENDATIONS

NNSs were introduced into the food supply to provide a noncaloric, sweet-tasting alternative to caloric sweeteners, which is useful for those with diabetes mellitus or who are avoiding sweet calories for other reasons, including obesity prevention and reduction. Concerns were initially raised about an association with cancer, but research in animal models and adult-human populations has shown no association between NNS use and cancer.[133] Some observational data in cross-sectional and prospective cohort studies in adults suggest that NNSs may promote obesity and metabolic syndrome but are subject to confounding and reverse causation.[26] Food challenge studies and short- and medium-term interventional data support a small benefit in weight maintenance or reduction in adults and children when NNSs are used as a substitute for caloric sweeteners. However, work remains to better understand the use of NNSs in toddlers, children, and adolescents in the general population and in at-risk populations (eg, diabetes, obesity, etc). Because of the ubiquitous presence of NNSs in everyday products and foods, it is unknown how much NNSs youth are consuming. Contemporary intake of NNSs (type and amount) and how they relate to ADI levels, specifically with regard to younger children, requires better and more detailed data. More information about the type and quantity of NNSs contained in various foods, beverages, and other products is recommended to better understand pediatric exposures. In particular, not only should the particular NNS contained in a product be noted as an ingredient, but the exact amount of any NNS within

a particular food item should also be included in the nutrition facts label.

KEY FINDINGS AND RECOMMENDATIONS

Findings and recommendations are as follows.

1. Current FDA-approved NNSs include saccharin, aspartame, acesulfame potassium, sucralose, neotame, stevia, and advantame. These agents are 180 to 20 000 times sweeter than sugar, potentially affecting preferences for sweet taste.
2. NNSs are designated either as food additives or as GRAS; the long-term safety of NNSs in childhood has not been assessed in humans.
3. No advice can be provided on the use of NNS in children younger than 2 years old given the absence of data on this age group.
4. The number of consumer products containing NNSs has quadrupled over the past several years; manufacturers must list NNSs in the ingredient list but are not required to indicate the amount per serving.
5. When substituted for caloric-sweetened foods or beverages, NNSs can reduce weight gain or promote small amounts of weight loss (~1 kg) in children (and adults); however, data are limited, and use of NNSs in isolation is unlikely to lead to substantial weight loss.
6. Individuals affected by certain conditions (eg, obesity and type 1 or 2 diabetes mellitus) may benefit from the use of NNSs if substituted for caloric sweeteners. However, health care providers should be aware that NNS use in isolation is unlikely to result in important weight loss, that observational studies show that NNS intake is associated with higher rates of metabolic syndrome and diabetes, and that a better understanding is needed about whether NNS use has a causal and harmful effect on metabolism and the risk of diabetes mediated through the gut microbiome or other as-yet-unidentified pathways.
7. To better inform the public about consumption of NNSs, the FDA should require products marketed in the United States to include labels that list the type and quantity of any NNS contained per serving of a product.
8. Funding should be allocated to encourage researchers to conduct high-quality research on the use of NNSs in childhood, focusing on age of exposure and taste preferences, neurodevelopment, and effect on the microbiome and its relevance to obesity, metabolic syndrome, and diabetes.
9. Health care providers are encouraged to remain alert to new information and sensitive to patient and family preferences.
10. With the exception of aspartame and neotame in children with phenylketonuria, there are no absolute contraindications to use of NNSs by children.
11. Use of NNSs has been associated with a reduced presence of dental caries.

GUIDANCE FOR PEDIATRICIANS

Primary health care providers should discuss with parents and patients (as appropriate) the available evidence regarding the benefits and harms of NNS use in children and adolescents. The AAP recommends that pediatricians discuss the following points with families.

1. NNSs are FDA approved for use in humans or are GRAS and, thereby, approved for use under the GRAS designation.
2. The GRAS designation is based on consumption of NNSs within an ADI level; it is not possible to measure an individual's daily intake of NNSs at this time.
3. Higher-quality data suggest that NNS use is associated with weight stabilization and/or weight loss in the short-term. Currently, there is a paucity of long-term data.
4. High-quality evidence, including meta-analysis and data from RCTs, suggests that there is no association between hyperactivity and NNS use in children.
5. There are limited data regarding the effect of NNS use on appetite change and taste preference.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
ADA: American Diabetes Association
ADHD: attention-deficit/hyperactivity disorder
ADI: acceptable dietary intake
AHA: American Heart Association
AND: Academy of Nutrition and Dietetics
CARDIA: Coronary Artery Risk Development in Young Adults
CI: confidence interval
FDA: US Food and Drug Administration
GRAS: generally recognized assafe
HR: hazardratio
NNS: nonnutritive sweetener
RCT: randomized controlledtrial
SSB: sugar-sweetened beverage
WC: waist circumference

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