Coca-Cola Health & Wellness Advisory Council

Position Statement on the Non-Nutritive Sweeteners Aspartame, Acesulfame K and Stevia

2015

EXECUTIVE SUMMARY

In 2010, the CCSP Health and Wellness Advisory Council (Appendix 1) prepared the 'Position Statement on the Non-Nutritive Sweeteners Aspartame, Acesulfame K and Stevia' which considered the safety and efficacy of these non-nutritive sweeteners. The position paper has now been updated following a review of published literature from June 2010 (Appendix 2). Key findings are as follows:

Safety

The non-nutritive sweeteners aspartame, acesulfame K and stevia have undergone extensive safety assessments by food regulatory authorities and are considered safe for use as general purpose, non-nutritive sweeteners in the general population.

In a comprehensive re-evaluation of the safety of aspartame conducted by the European Food Safety Authority in 2013, no issues of concern to the general population were identified and no changes were recommended to the Acceptable Daily Intake. In particular, EFSA ruled out a potential risk of aspartame causing damage to genes and inducing cancer based on an extensive review of both animal and human studies, and also concluded that aspartame does not harm the brain, the nervous system or affect behaviour or cognitive function in children or adults.

People with phenylketonuria (PKU) are advised to avoid products sweetened with aspartame. Products that are sweetened with acesulfame K and stevia, and are free of aspartame, can be safely consumed by people with PKU.

The available evidence does not support the hypothesis that aspartame-derived aspartic acid may lead to impairment of neurological function. Aspartame-derived methanol is very unlikely to pose any risk to health at intakes at or below the Acceptable Daily Intake for aspartame. The margin for safety is high.

Acesulfame K does not induce any effects of toxicological significance, even at very high intakes, nor does it have mutagenic or carcinogenic potential. There is no evidence that stevia is carcinogenic in animals or humans.

Body weight, appetite and sweet taste preference

The evidence on whether non-nutritive sweeteners affect appetite or preference for sweet foods is very limited and no firm conclusions can be drawn.

Recent randomised controlled trials indicate that the replacement of sugar-sweetened beverages with drinks containing non-nutritive sweeteners appears to be a useful adjunctive strategy for weight management, although no definitive long-term trials have been reported.

Diabetes and cardiometabolic risk

Aspartame, acesulfame K and stevia have no adverse effects on blood glucose or insulin levels and products containing these non-nutritive sweeteners may be safely included in the diets of people with diabetes. These sweeteners may be useful adjuncts to other weight control measures in people with diabetes. However, some caution derives from studies suggesting associations with type 2 diabetes and cardiovascular events, possibly reflecting other dietary and lifestyle confounders.

Dental health

Limited evidence suggests that the replacement of sugar-sweetened beverages with drinks sweetened with non-nutritive sweeteners may lower risk for dental caries. However, the acidity of some low-joule beverages confers risk for dental erosion.

CONTENTS

SAFETY ASSESSMENT OF NON-NUTRITIVE SWEETENERS

Food regulatory authorities have the responsibility for assessing all risks associated with the food chain in their respective countries and deciding which non-nutritive sweeteners are safe for human consumption, based on the scientific evidence available. Reassessments of non-nutritive sweeteners have occurred from time to time as new evidence relating to safety and community exposure became available. Regulatory agency reports are publicly available, consistent with policies of openness and transparency.

ASPARTAME

Aspartame was discovered in 1965 by chemist, James Schlatter who was working with G.D. Searle & Co in the USA. It was approved by the United States Food and Drug Administration for use in certain foods in 1974 and is one of the most widely used non-nutritive sweeteners as its taste is very similar to that of sucrose (table sugar).

Metabolism of aspartame

Aspartame is a dipeptide comprised of the amino acids aspartic acid and phenylalanine [1]. Animal and human studies have confirmed that once aspartame is consumed it is rapidly broken down into these amino acids and methanol. These are then absorbed into the bloodstream and used by the body for energy and building body tissues. As a consequence of its rapid breakdown, intact aspartame is not absorbed from the gut and cannot be detected in the bloodstream after ingestion by animals or humans [1].

Aspartic acid, phenylalanine and methanol are all found naturally in foods, such as fruit juices, meat and dairy products. These substances are often found in larger amounts in these foods than the amount that arises from the ingestion of foods and drinks sweetened with aspartame. For example, a glass of skim milk provides about six times more phenylalanine and thirteen times more aspartic acid, and a glass of tomato juice provides about six times more methanol, than an equivalent volume of beverage sweetened with aspartame [1].

Regulatory approval of aspartame

Aspartame has been approved for use in over 90 countries and is used in over 6000 types of food products and beverages worldwide [2]. The United States Food and Drug Administration approved aspartame for use in carbonated beverages in 1983 [3] and approved it for use as a general purpose sweetener in 1996. Approval was granted in some European countries in the 1980s and more widely in 1994 with the harmonisation of food regulations across the European Union. Aspartame was approved for use in Australia in 1986.

EFSA re-evaluation of aspartame (2013)

In 2013, the European Food Safety Authority (EFSA) published a comprehensive re-evaluation of the safety of aspartame as a food additive [4]. This detailed safety assessment considered animal experiments designed to assess the potential acute or chronic toxicity of aspartame, its carcinogenicity, and whether it has any adverse effects on reproductive performance, immune system function or neurological function. Human clinical studies, case reports and epidemiological studies were also considered, if available. These data were used to calculate the highest exposure that does not produce an adverse effect, called the no-observed-adverse-effect level (NOAEL). Safety factors were then applied to estimate the Acceptable Daily Intake (ADI) of the aspartame for humans. Prior to the EFSA re-evaluation the ADI for aspartame in Europe was 40 mg per kilogram of body weight per day, the same as that in Australia.

The findings of the review are discussed in detail below. More recent studies published since the EFSA review are also noted.

Safety studies of aspartame

- The EFSA report reviewed acute toxicity studies in several animal models [4]. These studies involved the administration of a single, very high dose of aspartame followed by monitoring for adverse effects. Typically, no physical, microscopic or haematological changes were observed, nor was there remarkable motor or behavioural activity, or deaths. The acute toxicity of aspartame was judged to be very low.

- Short-term and sub-chronic toxicity studies in several animal models were reviewed by EFSA. These studies involved the administration of repeated doses of aspartame, often at moderate levels, over a longer time period. Typically, no adverse clinical conditions or behavioural abnormalities were reported during the study period and survival was high in the treated groups, often 100%. Two papers by the same research group reported adverse effects on brain and liver antioxidant systems in rats [5,6]. EFSA concluded that the mild effects observed, the high doses of aspartame used in these studies and the small numbers of rodents involved raised questions about the relevance of these findings. Overall, the sub-chronic toxicity of aspartame was judged to be very low.

- The EFSA report reviewed the available *in vitro* and *in vivo* (animal) genotoxicity studies. The purpose of these studies was to assess whether exposure to aspartame results to damage to DNA, which has the potential to lead to cancer. EFSA concluded that the available data do not indicate a genotoxic concern for aspartame. Research in this field is ongoing [7].

- The EFSA report reviewed the available studies assessing the carcinogenicity of aspartame. These studies, conducted in a variety of animal models, assessed the effect on tumour incidence of the long-term administration of different doses of aspartame. EFSA concluded that cancer incidence in aspartame-exposed groups was not significantly increased in either sex compared to controls.

- EFSA reviewed the available reproductive and developmental toxicity studies. The purpose of these studies was to assess the effects of aspartame on sexual function and fertility in adult males and females, as well as any effects on the development of the offspring. The effects of L-phenylalanine were also tested in some studies. Reduced feed intake and maternal body weights were observed in some studies with high aspartame intakes. Whether this was a consequence of how the aspartame was administered or due to aspartame itself was difficult to ascertain. In support of the latter, reduced feed intake and maternal body weight was also observed with the administration of L-phenylalanine. Lower body weights in offspring fed large amounts of aspartame and L-phenylalanine were also observed in some studies. EFSA considered that it was plausible that L-phenylalanine derived from aspartame could be responsible for the effects reported for aspartame in these animal studies. Consequently, a conservative NOAEL for aspartame of 1000 mg/kg body weight/day was identified [4].

Safety studies of L-phenylalanine

In humans, high serum concentrations of L-phenylalanine are known to have adverse developmental implications. Humans with phenylketonuria (PKU) have a markedly reduced capacity for phenylalanine metabolism and consequently serum phenylalanine concentrations are high. If untreated, PKU babies show severe impairment in development and cognition. Adverse developmental effects have been observed in children born to PKU parents and these effects appear to be related to maternal serum phenylalanine concentrations. Based on these considerations EFSA concluded that L-phenylalanine is the main metabolite of concern in terms of potential developmental effects of aspartame in humans [4].

In characterising the risk associated with L-phenylalanine EFSA focussed on the plasma phenylalanine concentrations associated with developmental effects in children born from mothers with PKU, in preference to animal studies. Using current clinical guidelines as a guide to peak plasma phenylalanine concentrations and against a background of high dietary phenylalanine, EFSA modelled the responses to aspartame of normal subjects and PKU heterozygotes.

Humans heterozygous for PKU show a slightly reduced capacity to metabolise phenylalanine and slightly higher serum concentrations of phenylalanine after ingesting it, compared to normal individuals.

Based on this modelling EFSA concluded that aspartame was not of safety concern at the current aspartame exposure estimates or at the existing ADI of 40 mg/kg body weight/day, noting that a dose of approximately twice this figure, consumed over a period of eight hours by normal individuals, resulted in plasma phenylalanine levels in the normal post-prandial range. No changes were recommended to the existing ADI. The ADI is not applicable to subjects homozygous for PKU [4]. Such individuals or their carers would be aware of the metabolic disorder well before becoming exposed to aspartame-sweetened drinks.

Safety studies of methanol

As methanol is a metabolite of aspartame EFSA considered the possibility that any adverse health effects of aspartame may be mediated by methanol and reviewed all the available toxicological data [4].

- Although studies were limited, the reliable *in vitro* and *in vivo* data did not indicate a genotoxic potential for aspartame-derived methanol.
- Data for the assessment of the carcinogenic potential and the reproductive and developmental toxicity of aspartame-derived methanol were limited.
- A NOAEL based on inhalation studies in animals was established. This was over 100-fold higher than the maximum amount of methanol that could be released when aspartame is consumed at the ADI.
- Formaldehyde formed from the metabolism of aspartame-derived methanol was not considered a concern.
- EFSA concluded that aspartame-derived methanol is unlikely to pose any risk to health at intakes at or below the ADI of 40 mg/kg body weight/day.
- Since the publication of the EFSA report, a finding suggesting that aspartame-derived methanol may increase oxidative stress in the rat brain has been published [8].

Safety studies of aspartic acid

Neurotoxicity

Another aspartame metabolite, aspartic acid is a neurotransmitter and can be converted to glutamate, a more potent neurotransmitter. It has been suggested that aspartame-derived aspartic acid may lead to impairment of neuronal function, learning and behaviour, and lead to enhanced susceptibility to seizures and changes in behaviour and mood [9].

The potential of aspartic acid generated from aspartame to induce neurotoxicity has been investigated in a variety of animal models. These studies have been the subject of a previous review [2] and were reviewed again by EFSA [4].

EFSA's conclusions were consistent with those of the earlier review:

- The available evidence does not support the hypothesis that aspartame present in the human diet would cause any impairment of the neurological function.
- Aspartic acid generated from aspartame is not of safety concern at the current exposure estimates or at the ADI of 40 mg/kg body weight/day.

Since the publication of the EFSA report, two Egyptian studies by the same group found that repeated aspartame administration increased brain oxidative stress in mice [10,11].

Intake of aspartame

The most recent assessment of intakes of aspartame in Australia and New Zealand was published in 2004. Mean intakes were estimated to be 2.56 and 1.69 mg/kg body weight/day, respectively, both well below the ADI of 40 mg/kg body weight/day [12]. Among high consumers of aspartame (95th percentile) intakes are of the order of 13-23% of the ADI. Similarly low intakes have been recently observed in other populations [13,14]. Aspartame intake differs by age in Australia and New Zealand, with the 25-39 year-old age group being the highest consumers and the 12-17 year-old and over 60-year-olds consuming the least [12].

No data on trends in use of aspartame in Australia are available. In the United States, purchases of foods and beverages containing non-nutritive sweeteners increased during the 2000s as purchases of sugar-sweetened products declined [15,16].

Epidemiological studies of aspartame relating to safety

Cancer

- EFSA reviewed the evidence from case-control studies into the use of non-nutritive sweeteners (including aspartame) and cancer. Although little evidence was found suggesting aspartame was associated with cancer risk at any site, the quality of the studies was relatively poor and therefore also provided limited reassurance of safety. The Panel concluded that studies that suggested an association with cancer were generally flawed.

- EFSA found limited data from prospective cohort studies into aspartame and cancer. Lim and colleagues found no associations between aspartame intake and hematopoietic or brain cancers in a large US cohort [17]. Schernhammer and colleagues found associations between aspartame intake and both non-Hodgkin lymphoma and multiple myeloma in men, but not women [18]. EFSA placed little weight on these findings, given their limitation to men, the small relative risks observed and the lack of clear dose-response relationships [4].

- In summary, the EFSA review found negligible epidemiological evidence that the intake of aspartame was associated with increased cancer risk in humans.

Reproduction and child development

Pre-term delivery

- A large prospective cohort study conducted in Denmark found a small but significant association between consumption of soft drinks sweetened with non-nutritive sweeteners (including aspartame) and elevated risk of medically induced pre-term delivery, but not for spontaneous pre-term delivery [19]. Contrasting results were observed in a Norwegian cohort study [20].

- A meta-analysis of the findings from these two studies indicated similar risks of pre-term delivery with higher consumption both of sugar-sweetened soft drinks and drinks sweetened with non-nutritive sweeteners, suggesting residual confounding was at play [21].

- EFSA concluded that currently available epidemiological data do not suggest that consumption of beverages containing non-nutritive sweeteners (including aspartame) is a cause of pre-term delivery.

- EFSA noted that there was no risk to the human foetus from exposure to phenylalanine derived from aspartame at the current ADI (with the exception of women suffering from PKU).

Allergy

- A Danish cohort study found maternal consumption of beverages sweetened with non-nutritive sweeteners during pregnancy to be weakly associated with the incidence of asthma in offspring, though no exposure-response relationships were observed [22]. No associations with allergic rhinitis were observed.
- EFSA concluded that the findings could only be considered weakly suggestive of hazard and that more studies specifically related to aspartame were required.
- These epidemiological findings are consistent with those of a multi-centre placebo-controlled clinical study that found aspartame and its conversion products were no more likely than placebo to cause allergic symptoms in subjects thought to be sensitive to aspartame [23].
- EFSA concluded that the weight of evidence does not suggest that aspartame is associated with allergic-type reactions in humans.

ACESULFAME POTASSIUM (K)

Acesulfame K was discovered in 1967 by Hoechst scientists in Frankfurt, Germany, and has been used in food and beverages since 1983. It was approved for use in Australia in 1984. It is approximately 200 times sweeter than sucrose and is heat stable [24], allowing it to be used in cooking and baking, as well as a sweetener for foods and beverages. It provides no kilojoules. Acesulfame K is generally used in combination with other sweeteners as it can have a bitter aftertaste when used on its own [25]. When small amounts of acesulfame K are mixed with other non-nutritive sweeteners the resulting taste is similar to that of sucrose [26]. In Australia and New Zealand, acesulfame K is commonly used in combination with aspartame to sweeten carbonated beverages.

Metabolism of acesulfame K

Acesulfame K is rapidly and almost completely absorbed from the human gut. Maximum blood concentration is reached after 1-1.5 hours and thereafter elimination occurs rapidly. Only the parent compound can be identified in serum and urine, indicating that no significant degradation of acesulfame K occurs in the body [27].

Regulatory approval of acesulfame K

Acesulfame K is permitted for use as a sweetener in over 90 countries. The US Food and Drug Administration approved its use in dry food products in 1988 and in non-alcoholic beverages in 1998. The Joint FAO/WHO Expert Committee on Food Additives evaluated and approved acesulphame-K in 1983, giving it an ADI of 9 mg/kg body weight/d [28]. A higher ADI of 15 mg/kg body weight/d was adopted by the Food and Drug Administration in the United States in 1988 [29]. Acesulfame-K was approved for use in Australia in 1984, the ADI being 15 mg/kg body weight/d.

Safety studies of acesulfame K

The European Commission's Safety Committee on Food re-evaluated the safety of acesulfame K in 2000 following the publication of new safety studies [27]. Key findings were:

- Acesulfame K does not induce any effects of toxicological significance at dietary dose levels up to 3% in two different animal models.
- Acesulfame K is without mutagenic or carcinogenic potential.

Intake of acesulfame K

The most recent assessment of intakes of acesulfame K in Australia and New Zealand was published in 2004. Mean intakes of acesulfame K were estimated to be 0.53 and 0.39 mg/kg body weight/day, respectively, both well below the ADI of 15 mg/kg body weight/day [12]. Among high consumers of acesulfame K (95th percentile) intakes were of the order of 11-13% of the ADI. Similarly low intakes have been recently observed in other populations [13].

Acesulfame K intake differs by age in Australia and New Zealand, with the 25-39 year-old age group being the highest consumers, followed by the 18-24 year-old age group. Younger and older age groups consumed the least [12].

STEVIA

Stevia is the generic term for steviol glycosides, a group of sweet compounds extracted and purified from the herb Stevia rebaudiana. Stevia is a member of the Chrysanthemum family and the stevia leaf has been used as a sweetener for hundreds of years in South America. It is called "Ka'a He'e" ("Sweet Herb") in Paraguay.

The predominant steviol glycosides present are stevioside and rebaudioside A, which comprise 95% of the total. Stevia has zero calories and is 250-300 times sweeter than sucrose [30]. It has no effect on blood glucose levels. As steviol glycosides are heat stable, they are suitable for use in cooking and baking [31]. Stevia has a flavor enhancing effect when used in association with other flavours and may therefore be used in a wide range of food applications. Stevia contains no phenylalanine and therefore is suitable for use by people with phenylketonuria.

Metabolism of stevia

Once consumed, steviol glycosides are poorly absorbed from the human small intestine. However, steviol glycosides are hydrolysed by the microflora in the colon releasing steviol, which is absorbed and rapidly converted to steviol glucuronide and then excreted via the urine [32]. Free steviol does not appear in the plasma and neither steviol nor steviol glucuronide accumulates in the human body.

Regulatory approval of stevia

Stevia has been approved for use in Japan for over three decades and is the major non-nutritive sweetener used in that country. Food Standards Australia New Zealand assessed and approved an application for stevia in 2008 and subsequently increased permitted levels in foods [33]. The use of stevia as a food additive was authorised in the European Union in 2011 [34]. In the United States, the Food and Drug Administration has approved the limited use of stevia extract and stevia-based sweeteners.

Safety studies of stevia

The FAO/WHO Joint Expert Committee on Food Additives reviewed the safety of steviol glycosides in 2000, 2005, 2007 and 2009. These assessments formed the basis of the EFSA approval of stevia for use in the European Union in 2011 [34]. EFSA adopted a NOAEL of 967 mg/kg body weight/day and, after the application of a large safety factor, adopted an ADI of 4 mg/kg body weight/day. Key elements of this report are reviewed below, together with safety studies published since.

- Acute, short-term and sub-chronic toxicity studies in animals generally found no clinical signs of toxicity, no adverse changes in clinical chemistry, no changes haematology parameters and no deaths associated with the consumption of stevia. The one exception was reduced body weight in some studies, which was considered likely to have been the result of the palatability of the feeds with high concentrations of stevia [34].

- Although there is clear evidence that steviol is genotoxic *in vitro*, studies in several animal models show that the genotoxicity is not expressed *in vivo*, even at very high doses. Free steviol does not appear in the bloodstream of humans [34].

- There is no evidence that stevia is carcinogenic in animals or humans [34]. Anti-cancer effects have been reported in animal studies [35,36].

- A 2-generation study to assess reproductive and developmental toxicity of stevia found no adverse effects on reproductive function or reproductive organs at the highest dose fed. Reduced maternal body weights were observed in some studies but were thought to be related gastrointestinal effects of administering high levels of stevia rather than due to any toxic effect of the test compound. No treatment-related clinical signs were observed in the offspring [37].

- No adverse biological effects on blood pressure or glucose control have been reported in humans.

Intake of stevia

Estimated intakes of stevia for Australia and New Zealand are not currently available.

NON-NUTRITIVE SWEETENERS, BODY WEIGHT, APPETITE AND SWEET TASTE PREFERENCE

BODY WEIGHT

The consumption of beverages containing non-nutritive sweeteners has been associated with weight gain or increase in waist circumference in some [38-41], but not all [42,43], prospective cohort studies. This has led to suggestions that beverages containing non-nutritive sweeteners may be fuelling the obesity epidemic rather than ameliorating it. However, these cohort data need to be interpreted cautiously as reverse causality may be at play i.e. those at higher risk of weight gain may be choosing to consume beverages containing non-nutritive sweeteners in an attempt to control weight. In this instance, the consumption of beverages containing non-nutritive sweeteners would be a marker of people looking to lose weight rather than a behaviour leading to increased body weight over time. A further explanation would appear to be that consumers of drinks containing non-nutritive sweeteners show an overall low quality pattern of food selection and consumption [44].

Several recent meta-analyses have reviewed the results from observational prospective cohort studies and from randomised controlled trials that are the gold standard in trial hierarchy [45,46]. The observational cohort studies are generally inconsistent and too heterogeneous in their design to draw definite conclusions. Nevertheless, they suggest on average a small positive association with BMI, but not with fat mass, when measured. However, the conclusion from randomised controlled trials is for a modest weight loss when non-nutritive sweetened drinks are compared with sugar-sweetened drinks.

Two recent randomised controlled trials in adolescents and children are consistent with such a conclusion [47, 48]. The effects on body weight of replacing sugar-sweetened beverages with drinks containing non-nutritive sweetener were recently tested in a large randomised controlled trial in children [47]. After 18 months, weight gain and fat accumulation were lower in the children receiving beverages with non-nutritive sweetener. In a second randomised controlled trial, 224 overweight adolescents received a 1-year intervention designed to decrease consumption of sugar-sweetened beverages, primarily by displacing them with water and drinks containing non-nutritive sweetener [48]. After 12 months, body weight and body mass index were lower in the experimental group, though the differences were no longer significant at two years, showing that appropriate behaviour did not persist after the trial was completed.

These trials provide the strongest evidence yet that replacing sugar-sweetened beverages with beverages containing non-nutritive sweeteners has beneficial effects on body weight.

APPETITE

It has been suggested that the inconsistency between the intense sweet taste of non-nutritive sweeteners and the lack of energy that is consumed may lead to dysregulation of appetite control and, consequently, weight gain [49]. The potential of non-nutritive sweeteners to stimulate sweet taste receptors in the gut and possibly influence incretin hormone secretion is suggested as a possible mechanism [50].

Although there are some supportive animal data [51], the evidence from human studies does not suggest that non-nutritive sweeteners have adverse effects on appetite [52-54]. De Ruyter and colleagues found the opposite in a double-blind, randomised controlled trial – beverages with either sugar or non-nutritive sweeteners having the same effect on satiety despite the lower energy content of the non-sugar beverage [55].

SWEET TASTE PREFERENCE

It has been hypothesised that early taste experiences may underlie food acceptability and potentially appetite throughout the life span. Recent experiments in mice have shown that dietary exposure to acesulfame K in pregnancy or lactation enhances the preference for sucrose among the offspring [56]. Similar taste preferences are observed in adult mice exposed to acesulfame K shortly after weaning [57] and the development of taste buds is affected [58]. These studies are likely to generate more research into the possible effects of non-nutritive sweeteners on taste preferences and their implications for weight management.

In a 6-month randomised controlled trial, substituting sugar-sweetened drinks with either water or non-nutritive sweetened beverages did not increase the appetite for sweetened desserts [59].

NON-NUTRITIVE SWEETENERS AND DIABETES AND CARDIOMETABOLIC RISK

Several prospective cohort studies have found associations between the consumption of beverages containing non-nutritive sweeteners (as well as sugar-sweetened beverages) and increased risk for type 2 diabetes [60-62], the metabolic syndrome [63,64], hypertension [65], stroke [66] and coronary heart disease [67]. However, reverse causality may again be at play. In some of these studies positive associations between measures of cardiometabolic risk were observed with both sugar-sweetened beverages and drinks sweetened with non-nutritive sweeteners [60, 61, 65, 66]. Currently there are no plausible mechanisms that would explain the similar associations between both sugar-sweetened beverages and drinks containing non-nutritive sweeteners and measures of cardiometabolic risk. In the study by de Koning and colleagues, the positive association with risk for type 2 diabetes became non-significant after adjustment for dieting practices, baseline BMI, and health status, while the association between sugar-sweetened beverages and type 2 diabetes remained robust [60]. Methodological rigour will be essential in exploring these associations in future.

To date there have been relatively few randomised controlled trials assessing the effects of beverages containing non-nutritive sweeteners on cardiometabolic risk. Maersk and colleagues provided four different beverages to subjects in a 6-month trial and observed that the sugar-sweetened beverage resulted in increases in liver fat, visceral fat, blood triglycerides and total cholesterol compared to the drink containing non-nutritive sweetener, despite no change in total fat mass [68]. The beverage containing non-nutritive sweetener also lowered blood pressure by 10-15% compared to the sugar-sweetened drink.

A trial comparing stevia to placebo in subjects with type 2 diabetes found no effect on glucose homeostasis or blood pressure in individuals with type 2 diabetes mellitus [69].

More randomised controlled trials will need to be conducted before firm conclusions can be drawn on the effects of beverages sweetened with non-nutritive sweeteners on cardiometabolic risk.

In Australia and New Zealand, the consumption of non-nutritive sweeteners is more common in people with diabetes than in the general population, with aspartame being the most widely used sweetener [12]. In Australia, people with diabetes and impaired glucose tolerance consume more acesulfame K than their New Zealand counterparts [1]. As stevia was only permitted for use in foods and beverages by FSANZ in 2008, data on consumption of this sweetener by people with diabetes are lacking.

Aspartame has no effect on glycaemic control [70] or insulin levels [70,71] in people with diabetes. The effects of stevia on blood glucose appear to be the same as aspartame [72]. A small trial recently demonstrated that acesulfame K also has no effect on blood glucose or insulin levels [73].

NON-NUTRITIVE SWEETENERS AND DENTAL HEALTH

It is well established that frequent consumption of sugars such as sucrose can lead to increased risk for tooth decay. The replacement of sucrose in beverages and foods with non-nutritive sweeteners would therefore appear to have potential to lower this risk.

Early *in vitro* [74,75] and *in vivo* [75] studies are supportive. However, drinks containing non-nutritive sweeteners are still acidic (pH 2.5-4.5) and there is clear evidence that acid alone can erode tooth enamel when these drinks are sipped frequently [76]. The overall composition of the beverage should therefore be considered when assessing the impact of any product on dental health.

EVIDENCE-BASED MESSAGES

- The non-nutritive sweeteners aspartame, acesulfame K and stevia have undergone extensive safety assessments by food regulatory authorities and are considered safe for use as general purpose, non-nutritive sweeteners in the general population.
- Individuals with phenylketonuria should avoid products sweetened with aspartame. Products that are sweetened with acesulfame K and stevia, and are free of aspartame, can be safely consumed by people with phenylketonuria. No other group at risk from non-nutritive sweeteners has been identified.
- In Australia and New Zealand, intakes of non-nutritive sweeteners are low and well within Acceptable Daily Intakes, even among high consumers. Consumption is generally higher among middle-aged adults and lower among older and younger age groups.
- The consumption of beverages containing non-nutritive sweeteners has been associated with weight gain in some prospective cohort studies, giving rise to suggestions that these sweeteners may dysregulate appetite, promote a preference for sweet foods and contribute to obesity. However, reverse causality is a possible explanation in some cohort study findings.
- The evidence on whether non-nutritive sweeteners affect appetite or preference for sweet foods is very limited and no firm conclusions can be drawn.
- The replacement of sugar-sweetened beverages with drinks containing non-nutritive sweeteners is a useful adjunctive strategy for weight management.
- Aspartame, acesulfame K and stevia have no effect on blood glucose or insulin levels and products containing these non-nutritive sweeteners may be safely included in the diets of people with diabetes. These sweeteners may be useful adjuncts to other weight control measures in people with diabetes.
- The effects of non-nutritive sweeteners on cardiometabolic risk are unclear. Although associations between the consumption of non-nutritive sweeteners and the risk for type 2 diabetes, the metabolic syndrome, hypertension, stroke and coronary heart disease have been observed in several prospective cohort studies, potential mechanisms are lacking and reverse causality or confounding is a possible explanation.
- Limited evidence suggests that the replacement of sugar-sweetened beverages with drinks sweetened with non-nutritive sweeteners may lower risk for dental caries. However, the acidity of some low-joule beverages confers risk for dental caries.

REFERENCES

1. Butchko HH, Stargel WW, Comer CP, Mayhew DA, Benninger C, Blackburn GL, et al. Aspartame: review of safety. Regul Toxicol Pharmacol. 2002;35:S1-93.
2. Magnuson BA, Burdock GA, Doull J, Kroes RM, Marsh GM, Pariza MW, et al. Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. Crit Rev Toxicol 2007;37:629-727.
3. Food and Drug Administration. Food additives permitted for direct addition to food for human consumption: aspartame. Final rule. Fed Reg 1983. 48:31376-82.
4. European Food Safety Authority. Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive. EFSA Journal 2013;11(12):3496[263pp].
5. Abhilash M, Sauganth Paul MV, Varghese MV, Nair RH. Long-term consumption of aspartame and brain antioxidant defense status. Drug Chem Toxicol 2013;36:135-40.
6. Abhilash M, Paul MV, Varghese MV, Nair RH. Effect of long term intake of aspartame on antioxidant defense status in liver. Food Chem Toxicol 2011;49:1203-7.
7. Abd Elfatah AA, Ghaly IS, Hanafy SM. Cytotoxic effect of aspartame (diet sweet) on the histological and genetic structures of female albino rats and their offspring. Pak J Biol Sci 2012;15:904-18.
8. Iyyaswamy A, Rathinasamy S. Effect of chronic exposure to aspartame on oxidative stress in the brain of albino rats. J Biosci 2012;37:679-88.
9. Wurtman RJ. Aspartame: possible effect on seizure susceptibility. Lancet 1985;2:1060 (letter).
10. Abdel-Salam OM, Salem NA, El-Shamarka ME, Hussein JS, Ahmed NA, El-Nagar ME. Studies on the effects of aspartame on memory and oxidative stress in brain of mice. Eur Rev Med Pharmacol Sci 2012a;16:2092-101.
11. Abdel-Salam OM, Salem NA, Hussein JS. Effect of aspartame on oxidative stress and monoamine neurotransmitter levels in lipopolysaccharide-treated mice. Neurotox Res 2012b;21:245-55.
12. FSANZ. Consumption of intense sweeteners in Australia and New Zealand. Evaluation Report Series No. 8. 2004. http://www.foodstandards.gov.au/publications/documents/Intense_sweetener_Report_feb04.pdf
13. Diogo JS, Silva LS, Pena A, Lino CM. Risk assessment of additives through soft drinks and nectars consumption on Portuguese population: a 2010 survey. Food Chem Toxicol 2013;62:548-53.
14. Ha MS, Ha SD, Choi SH, Bae DH. Assessment of Korean consumer exposure to sodium saccharin, aspartame and stevioside. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2013;30:1238-47.
15. Ng SW, Slining MM, Popkin BM. Use of caloric and noncaloric sweeteners in US consumer packaged foods, 2005-2009. J Acad Nutr Diet 2012;112:1828-34.
16. Piernas C, Ng SW, Popkin B. Trends in purchases and intake of foods and beverages containing caloric and low-calorie sweeteners over the last decade in the United States. Pediatr Obes 2013;8:294-306.
17. Lim U, Subar AF, Mouw T, Hartge P, Morton LM, Stolzenberg-Solomon R, et al. Consumption of aspartame-containing beverages and incidence of hematopoietic and brain malignancies. Cancer Epidemiology, Biomarkers and Prevention 2006;15:1654-1659.
18. Schernhammer ES, Bertrand KA, Birmann BM, Sampson L, Willett WW, Feskanich D. Consumption of artificial sweetener- and sugar-containing soda and risk of lymphoma and leukemia in men and women. Am J Clin Nutr 2012;96:1419-1428.
19. Halldorsson TI, Strøm M, Petersen SB, Olsen SF. Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study in 59,334 Danish pregnant women. Am J Clin Nutr 2010;92:626-33.
20. Englund-Ögge L, Brantsæter AL, Haugen M, Sengpiel V, Khatibi A, Myhre R, et al. Association between intake of artificially sweetened and sugar-sweetened beverages and preterm delivery: a large prospective cohort study. Am J Clin Nutr 2012;96:552-9.
21. La Vecchia C. Low-calorie sweeteners and the risk of preterm delivery: results from two studies and a meta-analysis. J Fam Plann Reprod Health Care 2013;39:12-3.
22. Maslova E, Strøm M, Olsen SF, Halldorsson TI. Consumption of artificially-sweetened soft drinks in pregnancy and risk of child asthma and allergic rhinitis. PLoS One. 2013;8(2):e57261. doi: 10.1371/journal.pone.0057261
23. Geha R, Buckley CE, Greenberger P, Patterson R, Polmar S, Saxon A, et al. Aspartame is no more likely than placebo to cause urticaria/angioedema: results of a multicenter, randomized, double-blind, placebo-controlled, crossover study. J Allergy Clin Immunol 1993;92:513-20.
24. O'Brien-Nabors L. Sweet choices: sugar replacements for foods and beverages. Food Technol 2002;56:28-45.
25. Kuhn C, Bufe B, Winnig M, Hofmann T, Frank O, Behrens M, et al. Bitter taste receptors for saccharin and acesulfame K. J Neurosci 2004;24:10260-5.

26. Meyer S, Riha WE. Optimizing sweetener blends for low-calorie beverages. Food Technology 2002;56:42-45.

27. European Commission: Scientific Committee on Food. Re-evaluation of acesulfame K with reference to the previous SCF opinion of 1991. March 2000. http://ec.europa.eu/food/fs/sc/scf/out52_en.pdf

28. Joint FAO/WHO Expert Committee on Food Additives. Evaluation of certain food additives and contaminants. Twenty-seventh report. WHO Technical Report Series No. 696, 1983.

29. Food and Drug Administration. Food Additives Permitted For Direct Addition To Food For Human Consumption; Acesulfame Potassium. Federal Register Vol. 53. No. 145. July 28 1988.

30. Goyal SK, Samsher, Goyal RK. Stevia (Stevia rebaudiana) a bio-sweetener: a review. Int J Food Sci Nutr 2010;61:1-10.

31. Carakostas MC. Overview: the history, technical function and safety of rebaudioside A, a naturally occurring steviol glycoside, for use in food and beverages. Food and Chemical Toxicology 2008;46:S1-S10.

32. Wheeler A, Boileau A, Winkler P, Compton J, Prakash I, Jiang X, et al. Pharmacokinetics of rebaudioside A and stevioside after single oral doses in healthy men. Food and Chemical Toxicology 2008;46:S54-S60.

33. FSANZ. Application A1037 – Steviol Glycosides - Increase in Permitted Use Levels. Variation. 2011. http://www.comlaw.gov.au/Details/F2011L01415/Explanatory%20Statement/Text

34. EU Commission Regulation No 1131/2011. Steviol glycosides 11 November 2011 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:295:0205:0211:EN:pdf

35. Paul S, Sengupta S, Bandyopadhyay TK, Bhattacharyya A. Stevioside induced ROS-mediated apoptosis through mitochondrial pathway in human breast cancer cell line MCF-7. Nutr Cancer 2012;64:1087-94.

36. Ukiya M, Sawada S, Kikuchi T, Kushi Y, Fukatsu M, Akihisa T. Cytotoxic and apoptosis-inducing activities of steviol and isosteviol derivatives against human cancer cell lines. Chem Biodivers 2013;10:177-88.

37. Curry LL, Roberts A, Brown N. Rebaudioside A: two-generation reproductive toxicity study in rats. Food Chem Toxicol 2008;46 Suppl 7:S21-30.

38. Vanselow MS, Pereira MA, Neumark-Sztainer D, Raatz SK. Adolescent beverage habits and changes in weight over time: findings from Project EAT. Am J Clin Nutr 2009;90:1489–95.

39. BlumJW, Jacobsen DJ, Donnelly JE. Beverage consumption patterns in elementary school aged children across a two-year period. J Am Coll Nutr 2005;24:93–8.

40. Fowler SP, Williams K, Resendez RG, Hunt KJ, Hazuda HP, Stern MP. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. Obesity (Silver Spring) 2008;16:1894–900.

41. Nettleton JA, Lutsey PL,Wang Y, Lima JA,Michos ED, Jacobs DR. Diet soda intake and risk of incident metabolic syndrome and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2009;32:688–94.

42. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392–404.

43. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 2004;292:927–34.

44. Piernas C, Mendez MA, Ng SW, Gordon-Larsen P, Popkin BM. Low-calorie- and calorie-sweetened beverages: diet quality, food intake, and purchase patterns of US household consumers. Am J Clin Nutr 2014;99:567-77.

45. Pereira MA. Sugar-Sweetened and Artificially-Sweetened Beverages in Relation to Obesity Risk . Adv Nutr 2014;5:797-808.

46. Miller PE, Perez V. Low-calorie sweeteners and body weight and composition: a meta-analysis of randomized controlled trials and prospective cohort studies. Am J Clin Nutr 2014;100:765-77.

47. de Ruyter JC, Olthof MR, Seidell JC, Katan MB. A trial of sugar-free or sugar-sweetened beverages and body weight in children. N Engl J Med 2012;367:1397-1406.

48. Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL et al. A randomized trial of sugar-sweetened beverages and adolescent body weight. N Engl J Med 2012;367:1407-1416.

49. Ludwig DS. Artificially sweetened beverages. Cause for concern. N Engl J Med 2012;367:1397-1406.

50. Brown RJ, Rother KI. Non-nutritive sweeteners and their role in the gastrointestinal tract. J Clin Endocrinol Metab 2012;97:2597–605.

51. Davidson TL, Martin AA, Clark K, Swithers SE. Intake of high-intensity sweeteners alters the ability of sweet taste to signal caloric consequences: implications for the learned control of energy and body weight regulation. Q J Exp Psychol (Hove). 2011;64:1430-41.

52. Renwick AG, Molinary SV. Sweet-taste receptors, low-energy sweeteners, glucose absorption and insulin release. Br J Nutr 2010;104:1415-20.

53. Maersk M, Belza A, Holst JJ, Fenger-Grøn M, Pedersen SB, Astrup A, Richelsen B. Satiety scores and satiety hormone response after sucrose-sweetened soft drink compared with isocaloric semi-skimmed milk and with non-caloric soft drink: a controlled trial. Eur J Clin Nutr 2012a;66:523-9.

54. Steinert RE, Frey F, Töpfer A, Drewe J, Beglinger C. Effects of carbohydrate sugars and artificial sweeteners on appetite and the secretion of gastrointestinal satiety peptides. Br J Nutr 2011;105:1320-8.

55. de Ruyter JC, Katan MB, Kuijper LD, Liem DG, Olthof MR. The effect of sugar-free versus sugar-sweetened beverages on satiety, liking and wanting: an 18 month randomized double-blind trial in children. PLoS One. 2013 Oct 22;8(10):e78039. doi: 10.1371/journal.pone.0078039. eCollection 2013.

56. Zhang GH, Chen ML, Liu SS, Zhan YH, Quan Y, Qin YM, et al.. Effects of mother's dietary exposure to acesulfame-K in Pregnancy or lactation on the adult offspring's sweet preference. Chem Senses 2011;36:763-70.

57. Chen ML, Liu SS, Zhang GH, Quan Y, Zhan YH, Gu TY, et al. Effects of early intraoral acesulfame-K stimulation to mice on the adult's sweet preference and the expression of αgustducin in fungiform papilla. Chem Senses 2013;38:447-55.

58. Zhang GH, Chen ML, Liu SS, Zhan YH, Quan Y, Qin YM, et al. Facilitation of the development of fungiform taste buds by early intraoral acesulfame-K stimulation to mice. J Neural Transm 2010;117:1261-4.

59. Piernas C, Tate DF, Wang X, Popkin BM. Does diet-beverage intake affect dietary consumption patterns? Results from the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial. Am J Clin Nutr 2013;97:604-611.

60. de Koning L, Malik VS, Rimm EB, Willett WC, Hu FB. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. Am J Clin Nutr 2011;93:1321–7.

61. Fagherazzi G, Vilier A, Saes Sartorelli D, Lajous M, Balkau B, Clavel-Chapelon F. Consumption of artificially and sugar-sweetened beverages and incident type 2 diabetes in the Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale-European Prospective Investigation into Cancer and Nutrition cohort. Am J Clin Nutr 2013;97:517-23.

62. Sakurai M, Nakamura K, Miura K, Takamura T, Yoshita K, Nagasawa SY, et al. Sugar-sweetened beverage and diet soda consumption and the 7-year risk for type 2 diabetes mellitus in middle-aged Japanese men. Eur J Nutr 2014;53:251-8.

63. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. Circulation 2008;117:754-61.

64. Duffey KJ, Steffen LM, Van Horn L, Jacobs DR Jr, Popkin BM. Dietary patterns matter: diet beverages and cardiometabolic risks in the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am J Clin Nutr 2012;95:909-15.

65. Cohen L, Curhan G, Forman J. Association of sweetened beverage intake with incident hypertension. J Gen Intern Med 2012;27:1127-34.

66. Bernstein AM, de Koning L, Flint AJ, Rexrode KM, Willett WC. Soda consumption and the risk of stroke in men and women. Am J Clin Nutr 2012;95:1190-9.

67. Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. Am J Clin Nutr 2009;89:1037-42.

68. Maersk M, Belza A, Stodkilde-Jorgensen H, et al. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. Am J Clin Nutr 2012b;95:283–9.

69. Maki KC, Curry LL, Reeves MS, Toth PD, McKenney JM, Farmer MV, et al. Chronic consumption of rebaudioside A, a steviol glycoside, in men and women with type 2 diabetes mellitus. Food Chem Toxicol 2008;46 Suppl 7:S47-53.

70. Colagiuri S, Miller JJ, Edwards RA. Metabolic effects of adding sucrose and aspartame to the diet of subjects with noninsulin-dependent diabetes mellitus. Am J Clin Nutr 1989;50:474-8.

71. Okuno G, Kawakami F, Tako H, Kashihara T, Shibamoto S, Yamazaki T, et al. Glucose tolerance, blood lipid, insulin and glucagon concentration after single or continuous administration of aspartame in diabetics. Diabetes Res Clin Pract 1986;2:23-7.

72. Anton SD, Martin CK, Han H, Coulon S, Cefalu WT, Geiselman P, et al. Effects of stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels. Appetite 2010;55:37-43.

73. Wu T, Bound MJ, Standfield SD, Bellon M, Young RL, Jones KL, et al. Artificial sweeteners have no effect on gastric emptying, glucagon-like peptide-1, or glycemia after oral glucose in healthy humans. Diabetes Care 2013;36:e202-3.

74.. Giacaman RA, Campos P, Muñoz-Sandoval C, Castro RJ. Cariogenic potential of commercial sweeteners in an experimental biofilm caries model on enamel. Arch Oral Biol 2013;58:1116-22.

75. Brambilla E, Cagetti MG, Ionescu A, Campus G, Lingström P. An in vitro and in vivo comparison of the effect of Stevia rebaudiana extracts on different caries-related variables: a randomized controlled trial pilot study. Caries Res 2014;48:19-23.

76. Tahmassebi JF, Duggal MS, Malik-Kotru G, Curzon ME. Soft drinks and dental health: a review of the current literature. J Dent 2006;34:2-11.

APPENDICES

APPENDIX 1: MEMBERSHIP OF THE CCSP HEALTH AND WELLNESS ADVISORY COUNCIL

The Position Statement was developed by the Coca-Cola Health and Wellness Advisory Council, in July 2007, updated in June 2010 and more recently 2014.

The members of the CCSP Health and Wellness Advisory Council who critically reviewed the literature review and summary report to inform the update of the 2015 Position Statement are:

- Mr Glenn Cardwell, Director, Nutrition Impact
- Professor Peter Clifton, Head Nutritional Interventions, Baker IDI Heart & Diabetes Institute
- Professor Paul Nestel, Senior Principal Research Fellow and Senior Faculty, Baker IDI Heart & Diabetes Institute
- Professor Bernadette Drummond, Department of Paediatric Dentistry, Otago University

APPENDIX 2: METHODOLOGY FOR THIS REVIEW

Search Strategy

A search of the PubMed database was undertaken with the following search terms:

- Non-nutritive sweeteners
- Artificial sweeteners
- Aspartame
- Acesulfame K, Acesulfame Potassium
- Stevia, Stevia rebaudiana, Stevioside, Rebaudioside A
- Diabetes
- Cancer
- Blood pressure
- Blood glucose
- Appetite
- Satiety
- Body weight (regulation)
- Obesity/overweight
- Dental health
- Pregnancy
- Neurological (PKU, seizures)
- Children's health
- Dental health
- Safety
- Intake data

All *in vitro, in vivo*, safety/efficacy, animal and human studies published between June 2010 and November 2013 were eligible for inclusion. The only exclusion criterion applied was language other than English. Reviews were scanned for relevant studies.

Eighty-six publications were indentified in the search, of which 29 were review articles. All of these papers are listed in the report by Dr Fayet-Moore (July 2014). That part of the review relating to non-nutritive sweeteners and obesity/overweight was subsequently updated to include studies published up until December 2014. Another seven publications were identified.

In this report, reviews by food safety authorities were prioritised, in particular the major re-assessment of aspartame published by the European Food Safety Authority in 2013.