Mal J Nutr 22(1): 91 - 101, 2016

# Proceedings of the NSM Update Series: Sugar Substitutes- Understanding the Basics, Global Regulatory Approvals, Safety Assessment Protocols and Benefits

**Yashna Harjani[1], E Siong Tee[2] & Jimena Garcia[3]**

[1] *PepsiCo Inc. R&D Nutrition Science, Asia Pacific Region, Bangkok, Thailand*
[2] *Nutrition Society of Malaysia, Division of Human Nutrition, Institute for Medical Research, Kuala Lumpur, Malaysia*
[3] *PepsiCo Inc. Global R&D Nutrition Sciences, Mexico City, Mexico*

## ABSTRACT

A seminar titled "Sugar Substitutes: Understanding the Basics, Global Regulatory Approvals, Safety Assessment Protocols and Benefits" organised by the Nutrition Society of Malaysia was held on 15th April 2015 for nutritionists and other health care professionals, to review and discuss the latest evidence on safety and efficacy of sugar substitutes. Highlights from lectures by local and international speakers about this topical subject are presented in this report. Sugar substitutes have been extensively evaluated for decades and regulatory agencies world-wide continue to review and confirm their safety. Furthermore, the effects of sugar substitutes on human health continue to be the subject of research studies. Many studies have shown that replacement of sugar with sugar substitutes may help in weight management, glucose control for people with diabetes, and in the prevention of tooth decay. It is important for health professionals to discern whether the available evidence is based on good science and adequate protocols in order to guide consumers with the responsible use of sugar substitutes following national and international dietary guidelines. The use of sugar substitutes for certain health outcomes was discussed, specifically in regard to appetite, energy balance, body weight and other cardio-metabolic risk factors. Overall, the seminar provided an understanding of the different types of commercially available sugar substitutes, their use in a range of food and beverages, and calorie contribution to the diet. The seminar also covered the approvals of different sugar substitutes and the protocols for assessing the safety of these sugar substitutes, especially in the case of children and pregnant women.

**Key words:** Low calorie sweeteners, non-nutritive sweeteners, sugar substitutes, sweeteners

## INTRODUCTION

The use of sugar substitutes is a topic of discussion worldwide among both the general population and health care professionals. The current need to reduce sugar consumption as a strategy to tackle weight gain and non-communicable diseases has driven a vast offering of sugar substitutes. The food and beverage industries are using a range of sugar substitutes and blends to maintain a sweet taste but offer reduced sugar products. Organisations such as the American Diabetes Association and the Malaysian Dietitians Association support the use of sugar substitutes to reduce calorie intake, assist in weight and diabetes management, and prevent dental caries. The safety and

Correspondence: Yashna Harjani; Email: *Yashna.harjani@pepsico.com*

benefits of sugar substitutes have been extensively studied and approved by the main regulatory bodies around the world.

The seminar, held in Kuala Lumpur on 15th April 2015, and organised by the Nutrition Society of Malaysia in collaboration with PepsiCo Inc., provided a forum for dialogue between nutritionists and other health care professionals, academicians, food scientists, governmental agencies, policy makers, and the food industry.

This seminar gathered national and international experts to discuss the science of sugar substitutes. Dr. Tee E Siong[1] the President of the Nutrition Society of Malaysia, chaired the seminar and opened the session highlighting the fact that sugar substitutes are some of the most studied food ingredients worldwide, and have passed rigorous safety assessments. However, the awareness is limited and there are common queries among people about its health benefits and safety issues.

The seminar comprised different sessions presented by three speakers. Firstly, it provided an understanding of the different types of commercially available sugar substitutes, their use in a range of food and beverages, and calorie contribution to the diet. Next, the approvals of different sugar substitutes and the protocols for assessing the safety of these sugar substitutes, especially in the case of children and pregnant women was discussed. Finally the overall benefits of sugar substitutes were covered.

**Session I: Introduction to sugar substitutes and their use in food & beverages**

The first session saw Dr. Tee discussing sugar substitutes and their use in the general diet. The food and beverage indus--tries often innovate and renovate products to offer 'sugar-free' and 'diet' versions. These products use sweeteners that can be used to substitute regular table sugar or other nutritive sweeteners, and some have little or no calories. The terminology for sugar substitutes varies from artificial sweeteners, to low or non-caloric sweeteners or non-nutritive sweeteners.

The Mayo Clinic (2015) categorised sugar substitutes into four groups, namely: artificial sweeteners, sugar alcohols, novel sweeteners, and natural sweeteners.

Artificial sweeteners are synthetic sugar substitutes and add almost no calories to the diet. Examples include acesulfame potassium, aspartame, neotame, and saccharin. Artificial sweeteners are also known as intense sweeteners, as they are sweeter than sugar and can be used in very small amounts. For this reason, they are considered low-calorie or non-nutritive sweeteners due to the limited calorie contribution. For instance, the sweetening potency of acesulfame potassium and aspartame is 200 times greater than that of sugar, therefore only small amounts are required (Mayo Clinic, 2015). Artificial sweeteners are widely used to replace sugar in many processed foods and in home baking or cooking. However, the challenge is that when sugar is replaced with sweeteners, certain recipes have to be modified considerably, as these sweeteners do not have the bulk of sugar.

Despite the modifications required, artificial sweeteners are used in a broad range of food and beverages such as dairy products, diet soft drinks and fruit nectars, desserts, jams, confectionery, and chewing gum.

Sugar alcohols are carbohydrates that occur naturally in certain fruits and vegetables or can be manufactured; they include isomalt, erythritol, lactitol, maltitol, mannitol, and sorbitol. As sugar alcohols

[1] The collaboration does not imply endorsement of any products or brands by the Nutrition Society of Malaysia.

are not sweeter than sugar, and contain about half the calories of sugar, they are not considered non-nutritive sweeteners.

Sugar alcohols are generally used in combination with artificial sweeteners in processed foods such as chocolates, candy, frozen desserts, chewing gum, toothpaste, mouthwash, baked goods, and fruit spreads. Sugar alcohols add sweetness, bulk and texture to food; help food stay moist, prevent browning when heated, and add a cooling sensation to products.

Novel sweeteners, such as stevia extract and trehalose, are combinations of various types of sweeteners. Stevia is extracted from the leaves of the stevia plant which contains naturally sweet compounds called steviol glycosides. The different glycosides have sweetening potencies ranging from 30 to 400 times that of sugar, and they add almost no calories to the food or beverage. Stevia has been approved for use in many countries including Malaysia and can be found in many food and beverage products, including some juice and tea-based beverages, as well as some table top sweeteners.

Natural sweeteners include date sugar, fruit juice concentrate, maple syrup, and honey. Natural sweeteners are sugar substitutes that are often promoted as healthier options in contrast to processed table sugar. Nevertheless, many of these sweeteners are nutritionally similar to table sugar and are metabolised as glucose or fructose. Therefore, excessive intake of these sweeteners can lead to tooth decay, weight gain and increased triglycerides. In terms of perception, stevia is also referred to as a natural sweetener.

In regard to regulatory approvals, the Malaysian Food Regulations (1985) approved the use of a list of sweetening substances in food and beverages. This list includes artificial sweeteners (aspartame, acesulfame potassium, saccharin, sodium saccharin, sucralose, and neotame, stevia, and sugar alcohols (glycerol, isomalt, maltitol, maltitol syrup, mannitol, sorbitol, erythritol, and xylitol). The regulations also list the foods permitted to contain acesulfame potassium, neotame, and aspartame, and the maximum permitted levels for each food type

The Ministry of Health has proposed an amendment to the sugar substitute or sweetener regulation, to harmonise it with the General Standard for Food Additives (GSFA) of Codex Alimentarius (1989). In this proposed amendment, sweeteners are defined as a food additive other than a mono- or disaccharide sugar which imparts a sweet taste to a food. The proposed amended regulations have not yet been approved and published.

**Session II: Global Regulatory Approvals & Safety of Sugar Substitutes**

Dr. Berna Magnuson[2] summarised how the regulatory process for sugar substitutes begins at the international level with the safety assessment of sugar substitutes (categorised as food additives) conducted jointly by the World Health Organisation (WHO) and the Food and Agriculture Organisation of the United Nations (FAO) via the Joint FAO/WHO Expert Committee on Food Additives (JECFA). This assessment is based on an extensive safety evaluation and JECFA also establishes the acceptable daily intake levels for all approved sugar substitutes.

Dr. Magnuson listed some of the sugar substitutes already approved and available for use globally. These include intense sweeteners (e.g., advantame, acesulfame potassium, aspartame, cyclamate, monk fruit extract, neotame, saccharin, stevia extracts, and sucralose) and polyols (e.g., erythritol, isomalt, lactitol, maltitol, mannitol, polyglycerol, sorbitol and xylitol).

[2] Dr. Bernadene Magnuson, Associate Professor, University of Toronto, Canada

Dr. Magnuson described the extensive process of safety assessment starting with the definitions of safety and risk. A four-step process is used in the hazard evaluation of sweeteners. Firstly, sweeteners are assessed for absorption, distribution, metabolism, and excretion when consumed. Secondly, the long-term toxicity is assessed, Next other assessments such as impact on mutations, changes in the DNA and cancer development are assessed including toxicity during pregnancy and possible impacts on progeny such as the effect on their development. Finally, the effects on blood sugar or insulin levels based on human clinical studies are assessed.

In addition, Dr. Magnuson explained the differences between the specific levels of substances that are relevant for safety assessment.

No observed adverse effect level (NOAEL) is the level at which there is no adverse effect or no harm is observed in long term animal studies with daily consumption. A wide range of tests are used to define the level of consumption that produces no adverse effect during the different stages of the life cycle. Identification of the most important adverse effects and dose-response is used to define a level of consumption that produces no effect (Dorato & Engelhardt, 2005).

The Acceptable Daily Intake (ADI) is the amount that human populations can consume in the diet on a daily basis over a lifetime without an appreciable health risk. The ADI is established by regulatory agencies. It is based on the level that animals can consume every day without any adverse effect, and additional safety factors are then applied to this, to account for the differences among individuals and between humans and animals (Codex Alimentarius, 1989). Hence, the ADI level is always much lower than the NOAEL. For example, if the NOAEL for a substance is 1,000 mg/kg/day, and a 100-fold safety factor was applied, the ADI for that substance will be 10 mg/kg/day. This ensures that there is a very high degree of confidence that the ADI level is safe for the entire population. The safety factors ensure that the ADI applies to the entire population, including pregnant women and children. Moreover, the ADI is based on body weight, so the amount children consume is less than adults on a per person basis.

Additionally, the maximum permissible levels in food categories are set to ensure that their possible intakes do not exceed the ADI, even for high users regardless of age, sex, and special populations (e.g., people with diabetes and children).

Finally, the Estimated Daily Intake (EDI) for sweeteners has been assessed in multiple countries and is always found to be lower than the ADI levels. For instance, the NOAEL for aspartame is 4,000 mg/kg/day, the ADI is 40 mg/kg/day and EDI is 20 mg/kg/day for high users, and 2 to 5 mg/kg/day for average users. This demonstrates that even in high users, aspartame consumption is below the ADI. To achieve the ADI, a person weighing 70 kg would need to consume 80 packets of aspartame or 18 cans of soft drinks (12 oz or 355 ml) per day. The likelihood of people consuming aspartame at a level above the ADI seems unlikely.

All high intensity sweeteners approved for use by JECFA have been thoroughly tested, and the ADIs and maximum use levels have been established in foods and beverages to ensure that consumption is below the ADI for each sweetener. Moreover, the use of new sweeteners and mixtures lowers consumption of each sweetener, decreasing the probability of exceeding the ADI.

Dr. Magnuson also disccussed the lingering controversy surrounding the safety of sweeteners despite the rigorous safety assessments they are put through, and the difficulty of actually

reaching ADI levels. One of the reasons for this is that some adverse effects have been reported in animal experiments when very high doses were consumed. Additionally, inappropriate extrapolations and associations have been done in observational studies. In order to associate an exposure to a substance and a hazard, many factors should be considered with dosage being an essential factor.

In the same vein, Dr. Magnuson explained the relevance of the experimental protocol in the validation of the conclusions of a study. She shared examples of some of the studies whose conclusions have created controversy, explaining why they are not valid for humans.

1. In the case of saccharin, development of bladder cancer was observed in male rats when very high doses of saccharin were consumed (Price *et al.*, 1970). This was surprising as saccharin is neither mutagenic nor metabolised in the body. Follow up studies determined that this only occurred at very high doses in male rats, but neither in females nor in any other species. Furthermore, no link between saccharin and cancer development has been found in epidemiological studies in humans, including descriptive studies, cohort studies, and case-controlled studies. Therefore, it has been concluded that the effect on the bladder is specific only to the male rat at very high doses, and therefore not relevant to humans.
2. One study found a positive correlation between the consumption of diet soft drinks and waist circumference (Fowler, Williams & Hazuda, 2015) and concluded that diet sodas are associated with increased cardiovascular risk. However, no other diet information was collected and this study showed only association, but not any causal link. This is especially important in the aging population (≥ 65 yr ) that was studied, as many dietary factors have been well established to have an impact on health
3. A meta-analysis of fifteen randomised controlled studies also looked at the impact of low or no-calorie sweeteners (LNCS) on body weight and concluded that it can help support weight loss (Miller & Perez, 2014).
4. In other studies, aspartame was injected directly into the body of animals or added directly to cell culture (see review in Magnuson *et al.*, 2007). Such protocols are often invalid for food ingredients that are digested and absorbed in the gut. This study did not assess what actually happened with oral exposure. Aspartame as a whole does not enter the blood stream; it is completely digested in the gastrointestinal tract into three components, namely, amino acids, aspartate and phenylalanine (which are used for protein synthesis), and methanol (which is metabolised in the liver). Aspartame contributes only about 1% to 10% of the daily exposure to methanol (European Food Safety Authority [EFSA], 2013). Basal endogenous production of methanol and other dietary sources are major contributors to overall methanol exposure (Lindinger *et al.*, 1997).
5. In terms of aspartame and cancer, of the sixteen animal studies using multiple species of animals and various doses of aspartame conducted, fourteen studies found no evidence of carcinogenic effects and one study by Soffritti *et al.* (2007) reported positive results (Magnuson *et al.*, 2007). Upon careful review of data and protocols, EFSA and other organisations determined that the

methods used and the data from Soffritti's study were unreliable, as there were many problems with the study and reporting. They concluded that all credible evidence demonstrates that aspartame does not cause cancer. The most recent review of aspartame was completed in 2013 with the conclusion that aspartame is safe for everyone, including pregnant women, and there is no need to conduct further studies (EFSA, 2013).

6. Some individuals have claimed that aspartame consumption results in headaches and other sensitivities. To address these issues, a recent double-blind randomised cross-over trial was conducted to determine whether people who believed they were sensitive to aspartame experienced more symptoms following consumption of a snack bar containing either aspartame or no aspartame. The study found that the sensitive group reported more symptoms than the control group regardless of whether they consumed aspartame or not, and thus there was no evidence of sensitivity to aspartame (Sathyapalan *et al.*, 2015).

Dr. Magnuson then gave an overview of the metabolism of other intense sweeteners as described below:

*Sucralose* is structurally similar to sugar, but it cannot be broken down by digestion and 85% of it is not absorbed by the body. Sucralose is found in the faeces unchanged and only a small amount gets absorbed and excreted in the urine. Hence, safety concerns over it are limited (Grice & Goldsmith, 2000).

*Saccharin* is completely absorbed in the small intestine, is mostly excreted in urine, and only 5% is excreted in the faeces. Despite this fact, some studies have reported an adverse effect as discussed above. Nevertheless, the conclusion is that saccharin at the levels used in foods is safe for consumption and the overall evidence is that saccharin is safe to consume (Schoeffner & Thorgeirsson, 2000; International Agency for Research on Cancer [IARC], 1999).

*ASK or Acesulfame K* is commonly blended with aspartame to improve flavour and reduce the amount of sweeteners used. Though it is rapidly absorbed by the body, there are no safety concerns with *ASK*, because it is not metabolised by the body, and is excreted unchanged in the urine within 24 h (Renwick, 1986).

*Stevia or Steviol glycoside* is not digested or absorbed by the body. In the large intestine, the glucose units are removed by bacteria in the gut, resulting in steviol. Next, steviol is absorbed in the large intestine, modified by the liver and excreted (Carakostas *et al.*, 2008).

Finally, Dr. Magnuson emphasised that not everything that is 'natural' is safe and healthy. There are many naturally occurring compounds in foods that may also be hazardous and safety assessments have to be conducted for 'natural' substances too, if they are to be used as a food additive.

**Session III: Benefits & Concerns Linked to Sugar Substitutes**

Ms. Mageswary Lapchmanan[3] pointed out that Malaysia has the highest rate of overweight and obesity in Southeast Asia with the prevalence of overweight and obesity being 29.4% and 15.1%, respectively (Institute for Public Health, 2011), and associated with it, increased rates of diabetes and cardiovascular diseases (CVD). Sugar consumption in Malaysia is high as exemplified by their favourite drink, *teh tarik*, which contains 6 to 7 teaspoons of sugar, or 120 to 140 calories per glass.

[3] Ms. Mageswary Lapchmanan, Head of Department of Dietetics and Food Services, Hospital Selayang, Selangor

According to the Academy of Nutrition and Dietetics (AND, 2012), and WHO (2003), a higher intake of added sugars is associated with a higher energy intake and a lower diet quality, leading to weight gain and an increased risk of non-communicable diseases, as well as dental caries. The term 'added sugars' refers to other added sugars in addition to sucrose or table sugar. These added sugars can be anhydrous dextrose, brown sugar, confectioner's powdered sugar, corn syrup, corn syrup solids, dextrose, fructose, high fructose corn syrup, honey, invert sugar, lactose, malt syrup, maltose, maple syrup, molasses, nectars, pancake syrup, and raw sugar. As sugar is indirectly linked with many diseases, Ms. Lapchmanan reviewed the recommendations and guidelines by many organisations globally. The American Heart Association (AHA) recommends no more than 100 calories/day for women, and less than 150 calories/day for men from added sugars (Johnson *et al.*, 2009). The 2010 Dietary Guidelines for Americans (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2010) recommended reducing calories from added sugars. The Malaysian Dietary Guidelines (National Coordinating Committee on Food and Nutrition, 2010) also recommended consuming low sugar foods and beverages. In this regard, recently the WHO (2015) recommended that both adults and children reduce their intake of free sugars to 10% or rather to no more than 5% of the total energy intake, as a meta-analysis of studies suggested an association between the reduction of free sugar intake and reduced body weight (Te, Mallard & Mann, 2012).

The gap between the WHO recommendation and the consumption of some Malaysians implies that they need to cut down sugar intake by about 80%. However, the challenge is that all human beings have an innate desire for sweet flavours and are not willing to compromise on the pleasure of eating. Thus, sugar substitutes are perhaps the best solution to provide a sweet taste without the calories.

**Diabetes**

Malaysia is ranked fourth within Asia with regards to diabetes prevalence (Feisul & Azmi, 2013). Sugar substitutes can play a role in better blood sugar control in people with diabetes by providing sweetness with a limited amount of carbohydrates and calories. A systematic review of randomised control trials assessing the impact of sugar substitutes found that they did not impact glycaemic response (Wiebe *et al.*, 2011).

Based on existing evidence, the American Diabetes Association recommends that sugar alcohols and non-nutritive sweeteners are safe when consumed within the ADI levels established by the United States Food and Drug Administration (Gardner *et al.*, 2012). The Malaysian Dietitians Association (2015) also supports the view that non-nutritive sweeteners do not impact glycaemic levels. However, it is important to note that not all products labelled as 'sugar free' are consequently 'carbohydrate free' or 'calorie free'. The carbohydrate and natural sugar levels of all foods should be considered when planning a blood sugar management diet as part of diabetes or weight management.

**Weight management**

Different types of studies have explored the association between low calorie sweeteners (LCSs) and body mass index (BMI) and/or body weight. Prospective studies determined that LCSs had a small impact on the BMI, while no association was observed with body weight or fat mass (Miller & Perez, 2014). This negative association can be explained by the limitations of prospective cohort studies, such as the inadequate control of important confounders including total energy intake

and baseline differences between LCSs consumers and non-consumers in body weight and composition.

A meta-analysis of randomised control trials, which are better able to determine causality, found that LCSs have a modest but significant effect on body weight, BMI, fat mass, and waist circumference reduction (Miller & Perez, 2014). The AND (2012) concluded that the "use of aspartame and aspartame sweetened products as part of a comprehensive weight loss or maintenance program by individuals may be associated with greater weight loss and may assist individuals with weight maintenance over time." Additionally, many studies have found no evidence to support the idea that LCSs can contribute to an increase in body weight in children or in adults (Anderson *et al.*, 2012; Forey *et al.*, 2012). A meta-analysis of studies on adolescents assessing the impact of replacing sugared beverages with non-calorie ones found a decrease in calorie intake and BMI (with the adolescents who were most overweight at the beginning, experiencing the most improvement) versus their counterparts who drank sugary beverages (Ebbeling *et al.*, 2006). Thus, replacing sugary beverages with an alternative low / no calorie beverage should be considered by overweight teens.

Evidence linking LCSs with weight management indicates efficacy in short term studies but more evidence is needed in the long term (AND, 2011). Short term randomised control trials have determined a neutral effect on BMI and modest weight reducing effect with the use of LCSs in overweight and obese adolescents (Forey *et al.*, 2012).

Studies of adults that assessed the effect of sugar substitutes on weight, appetite and food, and nutrient intake have also determined that using sugar substitutes in place of sugary foods and beverages may help prevent unwanted weight gain (AND, 2011).

The use of LCSs may increase adherence to low calorie diets over time. This positive impact was attributed to the fact that as individuals were not deprived of sweet foods, they felt more satisfied with their eating plans and hence they were more likely to lose weight and keep it off (Anderson *et al.*, 2012).

Overall for a weight management plan, the key is a moderate calorie reduction, balanced diet and regular exercise. The inclusion of LCSs can help support a calorie reduction plan. Based on the current literature, it can be concluded that "substituting regular-calorie versions of food and beverages with LCSs options results in modest weight loss and may be a useful dietary tool to improve compliance with weight-loss and or weight-maintenance plans (Miller & Perez, 2014).

**Oral health**

Dental diseases are the most prevalent NCDs globally, and despite great improvements in prevention and treatment of dental diseases, problems still persist. Cohort studies in children suggest a positive association between the level of free sugar intake and dental caries. The evidence suggests higher rates of dental caries when the level of free sugar intake is greater than or equal to 10% of the total energy intake, compared with it being less than or equal to 10% of the total energy intake (WHO, 2015). Also, from a food perspective, in addition to free sugars, all carbohydrate foods can also contribute to tooth decay, as these provide a substrate for acid-producing bacteria that promote tooth decay (Touger-Decker & Van Loveren, 2003). When sugars are replaced with LCSs they are not fermented into harmful acids by oral bacteria. The substitution of sugars with LCSs is therefore beneficial for dental health, but it must be combined with good oral hygiene habits, regular dental check-ups, and exposure to fluoride (Navia, 1994).

**Cancer**

With regard LCSs and cancer, the National Cancer Institute (2009) supports the use of LCS as there is no clear evidence that acesulfame K, aspartame, neotame, saccharin, stevia and sucralose are associated with cancer risk in human beings.

**Other health effects**

The American Medical Association advises women to avoid saccharin during pregnancy, as the foetus may be unable to clear the substance quickly (Pitkin *et al.*, 1971). The AND (2012) on the other hand, expressed that a moderate intake of LCSs is advisable during pregnancy as the daily intake of beverages containing LCSs may be associated with an increased risk of preterm delivery. In the case of children, LCSs can safely be consumed in foods and beverages. Nevertheless, young children are not advised to restrict calorie intake unless advised by health care providers. There is no evidence that LCSs are linked with nervous system disorders and adverse behaviour, headaches, and allergies.

## SESSION CONCLUSIONS

The Malaysian Food Regulations (1985) approve the use of a wide list of sugar substitutes in food and beverages. LCS will continue being the subject of many studies. Nevertheless, study design, interpretation of results and consideration of all factors are critical for the assessment of the validity of their conclusions.

As limiting added sugars is important for optimal nutrition and healthy weight, sugar substitutes may be used in a structured diet as a tool to replace sources of added sugars. Additionally, the use of sugar substitutes versus a dietary restriction of all sweet food and beverages is more likely to increase dietary compliance in patients.

Artificial sweeteners and sugar substitutes may help in weight management and blood sugar control, but they are no 'magic bullet' and should be used in moderation within a balanced diet. Besides recommending the use of sugar substitutes, it is also important to educate patients about the different types of sugar substitutes, their role in the diet for weight and diabetes management, and adequate forms of consumption.

**Conflict of Interest**

The views expressed in the article are solely those of the authors and do not reflect the views of their respective institutions. Yashna Harjani and Jimena Garcia are employees of PepsiCo Inc.

## REFERENCES

Academy of Nutrition and Dietetics (2011). The Truth about Artificial Sweeteners or Sugar Substitutes. How Much is too Much? From Academy of Nutrition and Dietetics Evidence Analysis Library: *http://www.andeal.org/files/Docs/NNSResourceDraft3.pdf.* [Retrieved February 25 2015].

Academy of Nutrition and Dietetics (2012). Position of the Academy of Nutrition and Dietetics: Use of nutritive and nonnutritive sweeteners. *J Academy Nutr Dietetics* 112(5): 739-758.

Anderson G, Foreyt J, Sigman-Grant M & Allison D (2012). The use of low-calorie sweeteners by adults: Impact on weight management. *J Nutr*142: 1163S-1169S.

Carakostas M, Curry L, Boileau A & Brusick D (2008). Overview: The history, technical function and safety of rebaudioside, a naturally occuring steviol glycoside, for use in food and beverages. *Food Chem Toxicol* 46: S1-S10.

Codex Alimentarius (1989). Guidelines for the Simple Evaluation of Dietary Exposure to Food Additives CAC/GL-1989. Adopted 1989. Revision 2014. Retrieved from *file:///C:/Users/40017192/Downloads/cxg_003e.pdf.*

Dorato M & Engelhardt J (2005). The no-observed-adverse-effect-level in drug safety evaluations: Use, issues, and definition(s). *Regulatory Toxicol Pharmacol* 42(3): 265- 274.

Ebbeling C, Feldman H, Osganian S, Chomitz V, Ellenbogen S & Ludwig D (2006). Effects of decreasing sugar sweetened beverage consumption on body weight in adolescents: A randomised controlled pilot study. *Pediatrics* 117(3): 673-680.

European Food Safety Authority (2013). Scientific opinion on the re-evaluation of aspartame (E 951) as a food additive. *EFSA J* 11(12): 1-263.

Feisul M & Azmi S (2013). National Diabetes Registry Report 2009-2012. Kuala Lumpur. Retrieved from Ministry of Health Malaysia.

Foreyt J, Kleinman R, Brown R & Lindstrom R (2012). The use of low-calorie sweeteners by children: Implications for weight management. *J Nutr*146(2): 1155- 1162.

Fowler S, Williams K & Hazuda H (2015). Diet soda intake is associated with long-term increases in waist circumference in a bi-ethnic cohort of older adults: The San Antonio longitudinal study of aging. *J Am Geriatr Soc* 63(4): 708-15.

Gardner C, Wylie-Rosset J, Gidding S, Steffen L, Johnson R, Reader D & Lichtenstein A (2012). Non-nutritive sweeteners: Current use and health perspectives. A scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 35: 1798-1808.

Grice H & Goldsmith L (2000). Sucralose - An overview of the toxicity data. *Food Chem Toxicol* 38(Suppl 2): S1-S6.

Institute for Public Health (2011). National Health and Morbidity Survey 2011 (NHMS 2011). Vol. II: Non- Communicable Diseases. Institute of Public Health, Kuala Lumpur.

International Agency for Research on Cancer (1999). Saccharin and its salts. *IARC Monogr Eval Carcinog Risks Hum* 73: 517-624.

Johnson RK, Appel LJ, Brands M, Howard BV, Lefevre M, Lustig RH, Slacks F, Steffen LM & Wylie-Rosett J (2009). Dietary sugars intake and cardiovascular health: A scientific statement from the American Heart Association. *Circulation* 120(11): 1011-1020.

Lindinger W, Taucher J, Jordan A, Hansel A & Vogel W (1997). Endogenous production of methanol after the consumption of fruit. *Alcohol Clin Exp Res* 21(5): 939-943.

Magnuson B, Burdock G, Doull J, Kroes R, Marsh G & Pariza M (2007). Aspartame: a safety evaluation based on current use levels. *Regulations and Toxicological and Epidemiological Studies* 37: 629-727.

Malaysian Dietitians Association (2015). Artificial Sweeteners: Friend or Foe? From Malaysian Dietitians Association: *http://www.dietitians.org.my/health-info/artificial-sweeteners-friend-or-foe.* [Retrieved February 24 2015].

Malasyian Food Regulations (1985). From Food Safety and Quality Division, Ministry of Health Malaysia: *http://fsq.moh.gov.my/v4/images/filepicker_users/5ec35272cb-78/Perundangan/Akta%20dan%20Peraturan/Food_Regs_1985/FR1985_p8-sweetening.pdf.* [Retrieved March 12 2015].

Mayo Clinic (2015). Healthy Lifestyle: Nutrition and Healthy Eating. from Mayo Clinic. From: *http://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/artificial-sweeteners/art-20046936.* [Retrieved March 15 2015].

Miller E & Perez V (2014). Low-calorie sweeteners and body weight and composition: A meta-analysis of randomised controlled trials and prospective cohort studies. *Am J Clin Nutr* 100(3): 765-777.

National Cancer Institute. (2009). Artificial Sweeteners and Cancer: Questions and Answers. From National Cancer Institute Fact Sheet: *http://www.cancer.gov/cancertopics/factsheet/Risk/artificial-sweeteners.* [Retrieved September 17 2014].

National Coordinating Committee on Food and Nutrition (2010). Malaysian Dietary Guidelines. Ministry of Health Malaysia. Putrajaya: Technical Working Group on Nutrition Guidelines.

Navia JM (1994). Carbohydrates and dental health. *Am J Clin Nutr* Supplement 3: 719S-727S.

Pitkin R, Reynolds W, Filer L & Kling T (1971). Placental transmission and fetal distribution of saccharin. *Am J Obstet Gynecol* 111(2): 280-286.

Price J, Blava B, Oser B, Vogin E, Steinfield J & Ley H (1970). Bladder tumors in rats fed cyclohexylamine or high doses of a mixture of cyclamate and saccharin. *Science* 167(3921): 1131-1132.

Renwick A (1986). The metabolism of intense sweeteners. *Xenobiotica* 10-11: 1057-1071.

Sathyapalan T, Thatcher N, Harmmersley R, Rigby A, Pechlivanis A, Gooderham N, Holmes E, le Roux C, Atkin S & Courts F (2015). Aspartame sensitivity? A double blind randomised cross-over study. *PLoS One* 10(3): 1-13.

Schoeffner D & Thorgeirsson U (2000). Susceptibility of non-human primates to carcinogens of human relevance. *In Vivo* 14(1): 146-56.

Soffritti M, Balpoggi F, Tibaldi E, Degli Esposti D & Lauriola M (2007). Life-span exposure to low doses of aspartame beginning during prenatal life increases cancer effect in rats. *Environ Health Perspect* 115(9): 1293-1297.

Te Morenga L, Mallard S & Mann J (2012). Dietary sugars and body weight: Systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ* 346: e7492.

Touger-Decker R & van Loveren C (2003). Sugars and dental caries. *Am J Clin Nutr* 78(4): 881S-892S.

U.S. Department of Agriculture and U.S. Department of Health and Human Services (2010). Dietary Guidelines for Americans (7th ed.). U.S. Government Printing Office, Washington D.C.

Wiebe N, Padwal R, Field C, Marks S, Jacobs R & Tonelli M (2011). A systematic review on the effect of sweeteners on glycemic response and clinically relevant outcomes. *BMC Medicine* 9(123): 1-18.

World Health Organisation (2003). Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation. Geneva.

World Health Organisation (2015). Guideline: Sugars Intake for Adults and Children. Geneva.