SWEETNESS: ROLE OF SUGAR & LOW CALORIE SWEETENERS

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SWEETNESS: ROLE OF SUGAR & LOW CALORIE SWEETENERS

Conference held on September 20, 2017, New Delhi

International Life Sciences Institute-India

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Note: Presentations of Conference on " Sweetness: Role of Sugar and Low Calorie Sweeteners" are on ILSI-India Website: www.ilsi-india.org. Please visit the website for additional information.

Acknowledgements

A Conference on "Sweetness: Role of Sugar & Low Calorie Sweeteners" was organized by ILSI-India on 20 September, 2017 in New Delhi. A number of national and international experts presented their views. ILSI-India appreciates their contribution as also the suggestions from experts who participated.

The Conference was addressed by: **Mr. Pawan Agarwal**, (*CEO, Food Safety & Standards Authority of India, New Delhi*); **Mr. Sumit Arora**, (*Director, Client Leadership, Nielsen India, Gurugram*); **Dr. Joseph Lewis**, (*Expert, Food Regulations, Mumbai*); **Dr. Bernadene Magnuson**, (*Fellow, Academy of Toxicology Sciences, Canada*); **Dr. Ambrish Mithal**, (*M.D., D.M. Chairman, HOD, Division of Endocrinology and Diabetes Medanta, the Medicity, New Delhi*); **Dr. Akira Otabe**, (*General Manager, Scientific & Regulatory Affairs / Quality Assurance, Ajinomoto SEA Regional Headquarters Co. Ltd., Thailand*); **Dr. Seema Puri**, (*Associate Professor- Department of Nutrition, Institute of Home Economics, Delhi University, New Delhi*); **Mr. D H Pai Panandiker**, (*Chairman, ILSI-India, New Delhi);* **Dr. Ashley Roberts** (*Senior Vice President, Food and Nutrition Group Health, Environmental & Regulatory Services, Intertek, Canada*); **Prof. Peter Rogers**, (*Professor of Biological Psychology, School of Experimental Psychology, University of Bristol, UK*); **Dr. Priscilla Samuel**, (*Director, Global Stevia Institute & Director, Scientific & Regulatory Affairs, PureCircle, USA*); **Dr. Pradeep Saxena**, (*Additional Dy. Director General, Nutrition & IDD Cell, Dte. GHS, Ministry of Health & Family Welfare, GOI, New Delhi*); **Prof. P.K. Seth** (*NASI Senior Scientist Platinum Jubilee Fellow, Lucknow*); **Dr. Rekha Sharma**, (*President and Director, Nutrition and Dietetics, Diabetes Foundation (India), New Delhi*) and **Ms. Rekha Sinha**, (*Executive Director, ILSI-India, New Delhi*);

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The Monograph includes essence of the presentations and discussions at the conference.

Preface

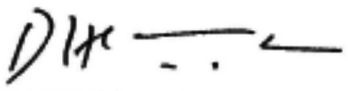
One of the undesirable side effects of economic progress is the increasing incidence of non-communicable diseases (NCDs) like diabetes, cardio vascular diseases or cancer. These result mainly from the changes in lifestyles and dietary habits.

Sugar is naturally present in a variety of foods like milk, fruits and vegetables. There is no reported evidence, however, about its adverse effects. It is the excess consumption of added sugar that is the cause of concern. Countries which are high in sugar consumption are also susceptible to high prevalence of NCDs. With the awareness about health risk from excess sugar consumption, a large number of people the world over have now shifted from sugar to sugar substitutes with similar sweetness but without the calories. The favored option is low calorie sweeteners (LCS).

ILSI-India has been organizing scientific conferences on sweetness to review the progress in science and keep track of new products and their benefits and safety, with the objective of helping the consumer make the right choices considering that, as recommended by WHO, sugar consumption should not exceed 10 per cent of the total energy intake or about 25 gms per day.

The third conference was held last September and was addressed by a number of renowned scientists. There was complete agreement in this session that LCS are safe and are the best option to sugar. They have been subject to intense investigations by international organizations like JECFA, which is an Expert Committee set up by FAO and WHO; as also by national regulatory authorities in US, Canada, European Union, Australia and so on. In India approvals are given by FSSAI.

The use of LCS is not as common in India as it is in most other countries. This may be due to restrictive use by people for managing NCDs rather than for possible prevention. There are also doubts and misconceptions about the adverse health effects of sweeteners. These were addressed in the conference and dispelled on the basis of scientific research investigations. I hope this monograph will be a useful guide to the public, policy makers and other stakeholders.



16th October 2017

D. H. Pai Panandiker
Chairman ILSI-India

Abbreviations

ADI	Acceptable Daily Intake
BMI	Body Mass Index
CVDs	Cardiovascular Diseases
EDI	Estimated Daily Intake
EFSA	European Food Safety Authority
FDA	Food and Drug Administration
FSANZ	Food Standards Australia/New Zealand
FSSAI	Food Safety and Standard Authority of India
GMP	Good Manufacturing Practices
HIS	High Intensity Sweeteners
ICMR	Indian Council of Medical Research
ICMR INDIAB Study	ICMR - IndiaDIABetes [INDIAB] Study
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LCS	Low Calorie Sweeteners
LDL	Low-Density Lipoprotein
NCD	Non-Communicable Diseases
NIN	National Institute of Nutrition
NOAEL	No-Observed-Adverse-Effect Level
RCT	Randomized Controlled Trails
SCFAs	Short-Chain Fatty Acids

Summary Findings

- **Research suggests** that liking for sweetness is innate and influenced by cultural and personal preferences. It is difficult to reduce sweetness in foods because of the entrenched habit and irresistible taste. In India sweets are an inevitable part of the celebrations whether at the festivals which are far too many or on other happy occasions.

- **With the awareness** about health risk from excess sugar consumption, a large number of people the world over have shifted from sugar to sugar substitutes with the objective of reducing weight by improving energy balance, managing diabetes and CVDs, and ensuring dental care. Consequently, the use of low calorie sugar free products has tripled over the last two decades. In the US for instance a recent report indicates that more than a quarter of children and two-fifths of adults consumeLow Calorie Sweeteners (LCS). Comparatively, in India their use in foods and beverages has been more recent but has been increasing at double digit rate in the past ten years.

- **LCS are safe** and their safety has been tested by robust means and all the data generated by scientific studies clearly indicates that above the age of one all, including children, pregnant and lactating women can consume LCS. Extensive reviews have been undertaken by regulatory authorities and committees such as The Joint FAO/WHO Expert Committee on Food Additives (JECFA), the United States (U.S.) Food and Drug Administration (FDA), the European Food Safety Authority (EFSA) and Food Standards Australia/New Zealand (FSANZ) and in India the Food Safety and Standards Authority of India (FSSAI).

- **JECFA** stringently evaluates sweeteners and those found to be safe for use are listed in the General Standards for Food Additives.(GSFA) published by Codex Alimentariun Commission. Safety is thus ensured for the consumer with the appropriate Average Daily Intake (ADI) for different sweeteners.

- **The ADI** "for man, expressed on a body weight basis, is the amount of a food additive that can be taken daily in the diet over a lifetime, without risk". The ADI may be used as benchmark to evaluate the actual intake of a substance and as an aid in reviewing possible additional uses for a food ingredient. The ADI is expressed in milligrams per kilogram of body weight.

- **The ADI** does not represent a maximum allowable daily intake level. It should not be regarded as a specific point at which safety ends and possible health concern begins. In fact:

    - **The U.S. FDA** has said it is not concerned about consumption levels occasionally exceeding the ADI . The agency has stressed that because the ADI has a built in safety margin and is based on a chronic lifetime exposure, occasional consumption in amounts greater than the ADI "would not cause adverse effects".

    - **The JECFA** has indicated "Because…data are extrapolated from lifetime animal studies, the ADI relates to lifetime use and provides a margin of safety large enough for toxicologists not to be concerned about short term exposure levels exceeding the ADI, provided the average intake over longer periods does not exceed it".

- **A large body of evidence** is required to support safety, and safety is critically reviewed by regulatory authorities.
- **Intakes of LCS remain below the ADIs.** Further, there is no evidence of adverse effects of LCS at levels of human consumption even within the highest users.Well conducted studies carefully reviewed by regulatory agency experts worldwide confirm lack of adverse health effects of consumption of LCS at approved use levels.
- **A number of controversies** have been reported regarding LCS. Careful examination of study design, interpretation of results and consideration of all factors is critical for assessment of validity of controversial studies. All regulatory authorities continue to support the safety of LCS. There is strong scientific evidence supporting safety of use of LCS.
- **Randomized controlled** studies have indicated that the concerns regarding LCS consumption and their association with cancer, changes in the gut microbiome, weight gain and over consumption of calories are unwarranted.
- **LCS were not designed** to control obesity. These can be used as a tool to manage it along with following an active and healthy lifestyle.

Recommmendations

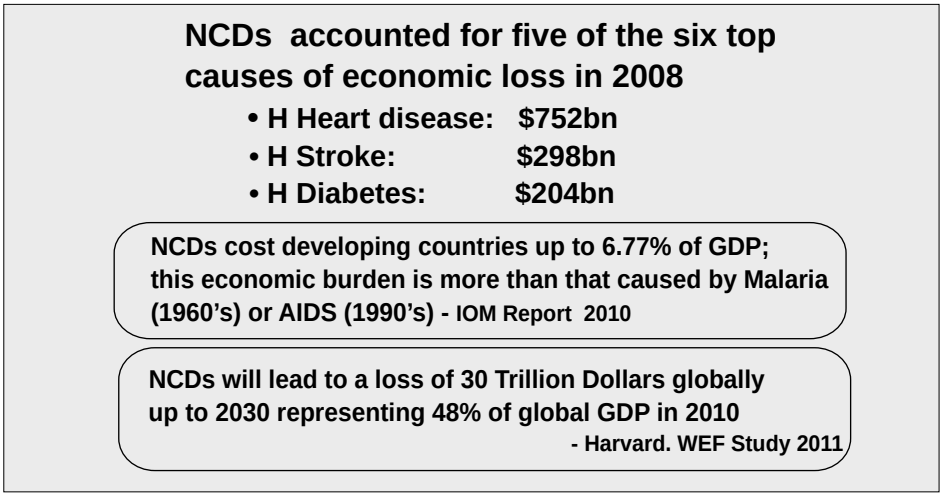
- **It is important to provide** correct knowledge to the consumers so that they can make informed choices regarding consumption of foods .
- **Information on the labels** should be correct and have short bytes like “safe to consume by all ages”. The Government agencies along with industry may need to join hands in changing this scenario.
- **Labelling advisory** on "Not recommended for children" should be reviewed as the risk assessment provided by JECFA and other risk assessment bodies (EFSA etc.) does not support this statement. Further, such an advisory promotes a perception that the product is not entirely safe.
- **FSSAI and other stakeholders** may use the terminology low calorie/no calorie/ high intensity sweeteners instead of “artificial sweetener” as this may help in improving their acceptability
- **In view of the above, labeling declaration** “ Contains artificial sweeteners” may be reviewed. The functional term is "sweetener' as provided in the food additive regulations FSS (2011), FSS (2016) and Codex. The term 'artificial sweetener' is in the labeling regulation. Nomenclature may be aligned in the impending labeling draft consistent with international practice.
- **Consumers** have to be told how much LCS can be consumed, in household measures /food measures, not ADI which cannot be understood by them
- **Media** can be used to create awareness. Schools, colleges, women's groups etc. can be directly approached for information dissemination. Acceptance can be achieved by working with health professionals like doctors, nutritionists and dieticians who are considered as trusted sources of information.
- **Multipronged approach** from industry/health professionals/food scientists in developing recipes is also needed.
- **Industry** has to come up with innovative blends to increase the palatability of the foods with LCS. Food scientists need to work on techniques which will improve the acceptability of foods with LCS and ensure that they are as near in texture and flavor to the original foods.
- **People** should also be cautioned that use of LCS may provoke a sense of complacency and drive them into eating other high calorie food more liberally. This should be avoided. Ultimately a healthy dietary lifestyle with physical activity is the answer to achieving good health.

Introduction

Non-communicable diseases (NCDs) pose major public health challenges undermining the socio-economic development of a nation. It is a matter of concern that India, the fastest growing economy in the world is facing an escalating epidemic of non-communicable diseases like diabetes, cardiovascular diseases, hypertension etc. This epidemic has been associated with both non modifiable factors like age, gender and heredity as well as the easily modifiable risk factors such as a faulty dietary pattern and unhealthy lifestyle practices including physical inactivity.The ICMR INDIAB study shows that the prevalence of diabetes is increasing in all parts of India, rural and urban, almost in parallel with economic development of states.

Data suggests that these disorders are happening among Indians not only in large numbers but also at a much younger age. Recent numbers from Delhi and Chennai (CAARS study) indicate a Diabetes prevalence of more than 20% at the age of 40 and almost 40% by the age of 60. And if 'Prediabetes' is included, the numbers reach an almost unbelievable 65% - 70%. These youngsters have to live with the disease for decades together, and include women in their reproductive age group, who still have not completed their families. All this is compromising on the productivity of our work force and impacting the economy.

Figure 1. NCDs Economic Impact



Source: Presentation by Dr Ambrish Mithal, The Medanta Medicity

Incidence of Overweight, Obesity, Hypertension and Diabetes in Urban Areas

The 2017 NNMB Report Series No. 27 on Urban Nutrition covering 1, 71, 928 individuals in 16 states reveals the following:

- Incidence of overweight and obesity (BMI>25) was 34% in men and 44% in women in the age group 15-49 years. According to WHO Asian cutoffs (BMI?23), 52% (CI-51.9-52.8) of men and 59% (CI-58.9-59.6) women were overweight and obese.
- The overall prevalence of hypertension (old and new cases) among men and women (18

years) was 38.5% (37.0-38.0) and 29% (29.0-29.8) respectively.

- The overall prevalence of diabetes (old and new cases) among men and women was 28.1% (27.4-28.7) and 23.3% (22.7-23.8) respectively.

- In general, more than twenty percent of both men (22.3% CI- 21.7-22.9) and women (22.4% CI- 21.9-22.9) were observed to have total high cholesterol levels (?200 mg/dl)which was found to be the highest in the age group of 50-70 years in both the genders. Similarly, 23% (22.4-23.6) men and 25% women (24.7-25.8) were observed to have high LDL cholesterol levels (?130 mg/dl).

- On an average, more than a fourth of urban men (28%) were doing physical exercise, mainly "walking" (21%), yoga (4%) and floor exercise (2%). Similarly, 15% of women were participating in physical exercise which included walking (11%) and yoga (3%). Among those who are having the habit of doing exercise, 23% of men and 12% of women were doing it daily.

Foremost causes of this emerging pandemic are modernisation, urbanisation, sedentary lifestyles and longevity. Major NCDs - cardiovascular diseases, diabetes mellitus, cancers and chronic respiratory diseases, share four common behavioural risk factors - tobacco usage, unhealthy diets, physical inactivity and harmful use of alcohol. The rapid shift from infectious diseases to NCDs is attributed to economic development coupled with transition from traditional healthy dietary patterns to refined/processed foods (high in total fat, trans fat, salt and simple sugars), physical inactivity, tobacco/alcohol abuse and changing socio-cultural norms. More than 80% of the cardiovascular diseases (CVDs)/type 2 diabetes mellitus (T2DM) and 33% cancers can be prevented through lifestyle modifications.

Strategy for Good Health

Any strategy that allows us to maintain ideal body weight, with better lean body mass, will prevent or delay onset of NCDs. Optimum nutrition and physical activity play a crucial role in maintaining good health. For leading a healthy life, the need for nutritionally/quantitatively balanced diet is known for centuries across various regions and cultures. Imbalanced energy intake has led to underweight/stunting at one end and over-weight/obesity/NCDs on the other. Therefore, "sustained energy balance" is critical in the maintenance of appropriate body weight and for ensuring optimal nutrient intake. Balanced diet provides appropriate proportions of proteins, fats, carbohydrates, minerals, vitamins and water needed for maintaining good health.

Carbohydrates which contributes nearly 60 en%, present wide range of qualitative differences. Consumption of highly refined carbohydrates forming major part of modern diet, need to be curtailed due to their high glycaemic index and thereby, elevating the NCD risk. Compared to poly/oligo-saccharides, intake of simple sugars needs to be curbed. It is difficult to remove the sweetness of sugar from our diets altogether as people can't do without sweet taste. Research indicates that weight reduction diets which are completely devoid of sugar, are not successfully followed. It has been advocated to keep the free sugar intake below 10 en% but poor palatability acts as the biggest impediment to such compliance.

Low calorie sweeteners (LCS) can offer a safe option for enjoying the sweetness without the calories. However, time and again questions have been raised about the safety of these LCS and their usage among different population groups. Although the usages of LCS have increased in India, yet people are concerned about their safety as well as their upper limits of consumption. This acts as a bottleneck in adopting this technological innovation for enjoying sweet taste without calories. It is necessary to examine how safety of LCS is established by international organizations like JECFA, whether there is any risk to any population group/s, examine the myths and facts associated with public perception and evolve a strategy for consumer education on use of sugar and sweeteners in day to day life to help them making healthy choices.

Nutritionally balanced diet as well as appropriate regular physical activity should be given due emphasis under the public health prophylactic measures so as to prevent and manage most of the cost intensive health problems. Maintenance of good health depends on wise management of energy from all the food/beverage sources along with a habit of regular physical activity. Given that very few individuals meet the physical activity recommendations, overall message regarding physical activity should likely be "the more the better".

Section 1
Importance of Sweetness

Sweetness is classically recognized as one of the five "basic tastes" detected by the sensory receptors present in the oral cavity. Research suggests that liking for sweetness is innate and influenced by cultural and personal preferences. While all humans express the same response to sweetness immediately after birth, the liking for sweet products changes with time and becomes highly idiosyncratic. As the child grows, the liking for sweetness changes. In adolescents, the preferred intensity of sweetness is lower than in younger children, and it is lower in adults than in adolescents. An appetite for sweetness is present in most adults, although large individual differences exist in both the preferred level of sweetness in familiar products and in the range of foods and drinks that are sweet.

Sugar, was invented in India. There is reference to sugarcane cultivation and preparation of sugar in the Atharva Veda. The word sugar is a derivative of "sarkara", meaning gravel in Sanskrit. Sugar became known to the world when the army of Alexander the Great came to India in 327 BC. They were surprised to see another alternative to honey to sweeten food, and described it as a "reed that gives honey without bees".

Traditionally, any joyous occasion, religious festival, social gathering in India is celebrated with intake of sweets. It is considered mandatory to offer sweets to the Gods on every religious occasion. While sugar is of considerable cultural relevance in India, nutritionally it provides only "empty" calories (1 g of sugar gives 4 kcal).

Sources of Sugar in Indian Diet

The added sugar in Indian diet comes from:

- *Sugar, honey, brown sugar, jaggery, khandsari.*
- *Traditional sweets.*
- *Bakery and confectionary – cakes, biscuits, chocolates, candies.*
- *Processed foods – breakfast cereals, salad dressings, spreads and sauces, aerated beverages.*
- *Hidden sugar - high fructose corn syrup, cane sugar, glucose, lactose, maltose, dextrose, malt syrup, molasses, agave nectar, maple syrup.*

The per capita consumption of sugar in India is 20.2 kg. It is lower than the global average of 24.8 kg, but consumption of sugar in India is growing more rapidly than the global average. However, in the last 50 years, sugar consumption in India has gone up from 5% to 13% of sugar produced globally. India has become the world's biggest sugar consumer today, consuming one-third more sugar than the entire E.U. and 60% more than China!

Indian sugar consumption is dominated by the industrial sector (61%) followed by the household (39%) or the consumer sector. The industrial sector includes companies that produce products which require sugar e.g. confectionary, carbonated beverages, dairy processing, bakery and others.

The household sector has been subdivided into lower and higher income groups. Total consumption of sugar by lower income group is 3.0 million tons and by higher income group is 1.4 million tons (FY'2015).Though per capita consumption in lower income groups is lower.

Figure 2. Sugar Consumption in India

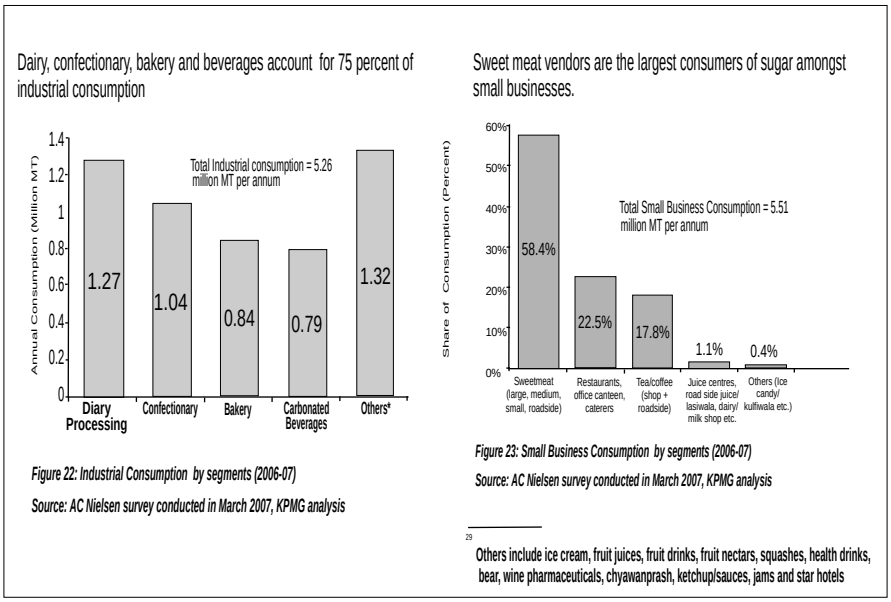


Figure 22: Industrial Consumption by segments (2006-07)

Source: AC Nielsen survey conducted in March 2007, KPMG analysis

Figure 23: Small Business Consumption by segments (2006-07)

Source: AC Nielsen survey conducted in March 2007, KPMG analysis

[29] Others include ice cream, fruit juices, fruit drinks, fruit nectars, squashes, health drinks, bear, wine pharmaceuticals, chyawanprash, ketchup/sauces, jams and star hotels

Source: Presentation by
Dr Seema Puri, Institute of Home Economics, University of Delhi

Dietary Guidelines for Sugar Consumption

Consumption of excess sugar is linked to NCDs. WHO and various other scientific bodies have laid down limits for consumption of added sugar.WHO strongly recommends a reduced intake of free sugars throughout the life course. Further, in both adults and children, WHO recommends reducing the intake of free sugars to less than 10% of total energy intake; and a further reductionin intake of free sugars to below 5% of total energy intake. The WHO guideline do not refer to the sugars in fresh fruits and vegetables, and sugars naturally present in milk, because there is no reported evidence of adverse effects of consuming these sugars. The sugars guidelines should be used in conjunction with other nutrient guidelines and dietary goals, in particular those related to fats and fatty acids, including saturated fat and trans-fat.

In India, the National Institute of Nutrition recommends an added sugar intake of not more than 20 to 25 gm a day for normal adults. The Consensus Dietary Guidelines for Indians recommend less than 10% of total calories from free sugars per day.

Section 2

What are low Calorie Sweeteners ?

Low calorie sweeteners (LCS) provide a solution to reducing the sugar intake without sacrificing the sweet taste. They are sugar substitutes that have zero/negligible calories and do not raise blood glucose levels upon consumption. They are added to various type of food and beverages to impart a sweet taste with fewer calories or without calories. Low calorie sweeteners may be further classified as bulk sweeteners and high intensity sweeteners (HIS).

The main compounds used as bulk sweeteners are sugar alcohols, such as sorbitol and maltitol. Bulk sweeteners are used when functional characteristics of sugar are required as these have physical properties that contribute to the structural and sensory characteristics of food like sugar. The categories for which bulk sweeteners are most commonly used are bakery, snacks, sugar and gum confectionery, and desserts and ice-cream and even traditional Indian sweets. Considering percentage of food and drink containing bulk sweetener launched from 2011 to 2016, sorbitol is most commonly used bulk sweeteners followed by maltitol and xylitol.

Commonly used LCS/HIS are: acesulfame-potassium, aspartame, cyclamates, saccharin and sucralose. LCS/HIS are now used in a wide range of foods, not just beverages and the consumption is growing especially in the Asia Pacific Region.

Most of the LCS/HIS (hereinafter called LCS) sweeteners have an intense sweet taste, several hundred times more than sugar, hence only small quantities need to be added to obtain the normal sweet taste. This provides very little or negligible calories

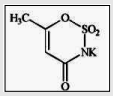
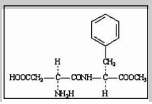
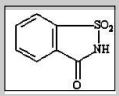
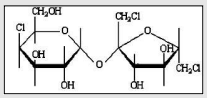
Table 1. Mg of LCS to Replace Grams of Sugar

Sweetener	Sweetness Intensity (compared to sucrose)	Amount to replace 100 calories or 25 g of sugar
Acesulfame K	~ 200x	125 mg
Aspartame	~ 200x	125 mg
Cyclamate	~ 30x	800 mg
Saccharin	~ 300x	80 mg
Sucralose	~ 600x	40 mg
Steviol glycosides	200-300x	80 -125mg

Source: Presentation by Dr. Bernadene Magnuson, Academy of Toxicological Sciences

Today, there are several LCS available in the market. These have been approved by FAO / WHO Joint Expert Committee on Food Additives (JECFA), regulatory authorities in different countries like US FDA, EFSA and in India by the FSSAI.

Table 2. Commonly Used High Intensity Sweeteners (HIS) / LCS

	Sweetness*	Acceptable Daily Intake by JECFA	Approval status
Acesulfame K 	**130 – 200**	**15 mg/kg b.w. (1990)**	**Approved in more than 100 countries**
Aspartame 	**200**	**40 mg/kg b.w. (1981)**	**Approved in more than 100 countries**
Cyclamate 	**30** – 50	**11 mg/kg b.w. (1982)**	**Approved in more than 50 countries**
Saccharin 	**300** – 500	**5 mg/kg b.w. (1993)**	**Approved in more than 90 countries**
Sucralose 	**600**	**15 mg/kg b.w. (1990)**	**Approved in more than 80 countries**

*** Comparative value when sweetness of sucrose is 1.**

Source: Food and Sweeteners (Korin Book, 2008); Fact Sheet (International Sweeteners Association)

Source: Presentation by Dr. Akira Otabe, Ajinomoto SEA Regional Headquarters

Trends in Consumption of LCS/HIS

- LCS market is estimated to grow rapidly in Asia-Pacific region.
- Saccharin is most dominant in terms of consumption level with sugar equivalent, but main category for which it is used is for pharmaceutical.
- Usage of sucralose is growing in worldwide and aspartame and acesulfame K in Asia-Pacific region.
- LCS is commonly used in beverage in all areas worldwide.
- Usage of LCS in food category is growing in Asia-Pacific and almost comparable to beverage use.
- LCS/HIS in India (2018) is 8% of Asia-Pacific.
- In India 70% of LCS/HIS is used for pharmaceutical. Usage in beverage, food and table top is small.

Two new LCS which have been recently introduced are: neotame and advantame. The sweetness compared to sugar is very high i.e. they are respectively 8000 and 30000 sweeter compared to sugar. Although advantame has been approved in just 10 countries as of now, neotame has been approved for use in over 60 countries.

There has been some concern about the taste profile of the LCS when compared to sugar. Although, LCS may have a different profile of taste from sugar; this problem can be solved by combination of one or more LCS as it also enhances development of sugar free/ energy reduced food products. It would provide long lasting sweetness, enhance flavours and even mask certain flavours.

Stevia is another LCS gaining prominence as it is derived from a plant and thus can be said that it is 'naturally' sourced. It has been used since centuries by indigenous people of Paraguay to sweeten their foods. It has now been processed scientifically to extract it's sweet compound called Steviol Glycosides. These are now being marketed as tablets or powder form. It can be used as an effective alternative to sugar to control calorie intake, decrease blood sugar and manage weight. Scientific bodies like the AHA and ADA have also expressed that consumption of stevia is safe and may be used as a sugar alternative. It can be used in beverages and in fruit juices.

Indian Regulations on LCS

Food additives and their use is controlled by specific regulations by FSSAI. The Food Safety and Standards (Food Product Standards and Food Additives) Seventh Amendment 2016, is a significant amendment to the erstwhile regulations harmonized with international practice. It lists those sweeteners only that are determined to be safe and introduces the Food Category System that classifies all foods in a hierarchical order and organizes allotment based on category descriptors and the acceptable daily intake (ADI). The regulation applies to all foodstuffs whether standardized or not, including foods to which additives should not be added. The following LCS are approved for use in India:

- **Non-caloric (non-nutritive) sweeteners:** Acesulfame- Potassium, Aspartame, Saccharin, Sucralose, Neotame, Thaumatin, Alitame, Mixed Salt of Aspartame-Acesulfame Potassium, Steviol Glycosides and others are progressively included for use in foods under applicable conditions.
- **Low caloric sweeteners (nutritive), with lesser calories than sugar:** referred to as sugar alcohols, they include Isomalt, Lactitol, Mannitol, Maltitol, Erythritol. These may be generally added to foods (with exceptions) according to good manufacturing practice (GMP).

Low calorie sweeteners must comply with purity specifications as provided in regulatory texts or recognized sources. The addition of sweeteners to foods, pre-packaged for sale, require compliance with several label declarations such as ingredient listing or provide advisory statements:"contains artificial sweeteners and for calorie conscious", "not recommended for children", "not for phenylketonurics", "or may have laxative effect", as appropriate and emphasized by a surrounding line.

Dietary interventions are required to reduce intakes of certain nutrients implicated in non-communicable diseases (NCD's). Several types of interventions are available ranging from advocacy, education, regulatory and technological. Of these, the use of low calorie sweeteners in food is a viable technological intervention for reducing dependence on sugar and reducing calories. Low calorie sweeteners are major alternatives to sugar.

Section 3
Safety of Low Calorie Sweeteners

The safety of all food additives such as low/no calorie sweeteners is assessed by extensive reviews undertaken by regulatory authorities and committees such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the United States (U.S.) Food and Drug Administration (FDA), the European Food Safety Authority (EFSA) and Food Standards Australia/New Zealand (FSANZ) and in India the Food Safety and Standards Authority of India (FSSAI).

Prior to providing an approval and authorization for any sweetener, a comprehensive database has to be developed for a sweetener and safety assurance is primarily based upon toxicological (both in vitro and in vivo) and clinical studies. These studies include short-term tests for mutagenicity and genotoxicity, absorption and metabolism (pharmacokinetics), sub-chronic studies, chronic toxicity, cancer bioassays and reproduction and developmental studies and teratogenicity. Comprehensive batteries of studies are conducted in multiple species. Studies are also conducted on humans especially for diabetes. What is most important to note is that all data from all studies has to be reviewed by the regulatory authorities. It is not acceptable to only file the positive studies while ignoring negative data (WHO, 2009a,2009b).

Safety assurance is based on studies in animals given very high doses. The main aim of such studies is to produce:

1. potential adverse effects in the test species, and
2. define a daily intake without adverse effects (NOAEL)

Low calorie sweeteners are some of the least toxic compounds which allow dosages up to 10% of the diet in some cases to replace the basal diet. While such dosages are equivalent to very high human exposure levels (most likely to be not reached in the lifetime of the individual) these are considered important for human safety assurance.

Table 3. Exposure Levels are Very Low Due to High Sweetness Potencies

Sweetener	Sucrose sweetness equivalence	ADI (mg/kg bw/d)	Maximum daily mg intake based on 70kg person
Acesulfame	**200 x**	15	1050
Aspartame	**200 x**	40	2800
Saccharin	**400 x**	5	350
Sucralose	**600 x**	15	1050
Steviol Glycosides	**~300 x**	4	280

Source: Presentation by Dr. Ashley Roberts, Intertek

Based on these high doses, companies/industry establishes a no-observed-adverse-effect level (NOAEL) from the longer-term chronic assays in the most sensitive species for a new sweetener/additive. The NOAEL from the animal studies is converted to an acceptable daily intake (ADI) by dividing it with a default uncertainty factor, usually 100, to allow for potential differences between test animals and humans.

Average Daily Intake (ADI)

The ADI has been defined by JECFA as "An estimate of the amount of a food additive, expressed on a bodyweight basis that can be ingested over a lifetime without appreciable health risk".

The ADI is usually expressed as a numerical value in mg/kg bw/day. The ADI has been used for the past 50 years to establish safe intakes of food additives including LCS.While JECFA determines ADI's, food additives such as LCS are on a positive list that have to be formally approved to be on that list. These additives are reassessed when new data becomes available (e.g.,Ramazzini) or as part of a cyclic review such as is going on in the EU now for LCS.

Calculation of ADI's

ADI (mg/kg/day) = NOAEL/safety factor which is usually to account for differences between individuals (10 X) and differences between humans and animals (10 X). Toxicological protocols adopted for LCS cover all periods of rapid growth and development maturation and aging and therefore all circumstances of human exposure. Exposure during the juvenile period is taken into account and so the ADI applies to children as well. The only exception is for infants below 3 months of age. Due to lower levels of metabolising enzymes and also because studies do not mimic babies receiving infant formula in a unitary diet.

What is important to note is that the ADI is not a lower bound of toxicity as there is at least a 100-fold safety margin. Given that LCS are some of the least toxic substances and show little if any acute toxicity, so day to day variations in intake are not relevant for human health and safety.

The ADI does not represent a maximum allowable daily intake level. It should not be regarded as a specific point at which safety ends and possible health concern begins. In fact, the U.S FDA has said it is not concerned about consumption levels occasionally exceeding the ADI .The agency has stressed that because the ADI has a built in safety margin and is based on a chronic lifetime exposure, occasional consumption in amounts greater than the ADI "would not cause adverse effects".

The JECFA has indicated "Because…data are extrapolated from lifetime animal studies, the ADI relates to lifetime use and provides a margin of safety large enough for toxicologists not to be concerned about short term exposure levels exceeding the ADI, provided the average intake over longer periods does not exceed it". In reality the risk associated with the ADI being exceeded can only be assessed

based upon the NOAEL and the dose response curve. As stated previously LCS are some of the least toxic substances and show little if any acute toxicity and so day to day variations in intake are not relevant for human health and safety.

Re-Evaluation Process

Not only are these sweeteners subjected to intense scrutiny, in the European Union LCS permitted/approved before 20 January 2009 are required to undergo a thorough new risk assessment by the European Food Safety Authority (EFSA). Therefore other than aspartame, advantame and steviol glycosides all LCS including acesulfame K, alitame, cyclamate, neotame, nHDC, sucralose and thaumatin will be re-evaluated by March 2018 and will be evaluated again by 2020. Thus, the process of assessing the safety is dynamic and subject to re-evaluation based on newer data.

Section 4
Busting the Myths

Although the safety of LCS has been proved time and again, yet there are certain questions which are always raised regarding their use.

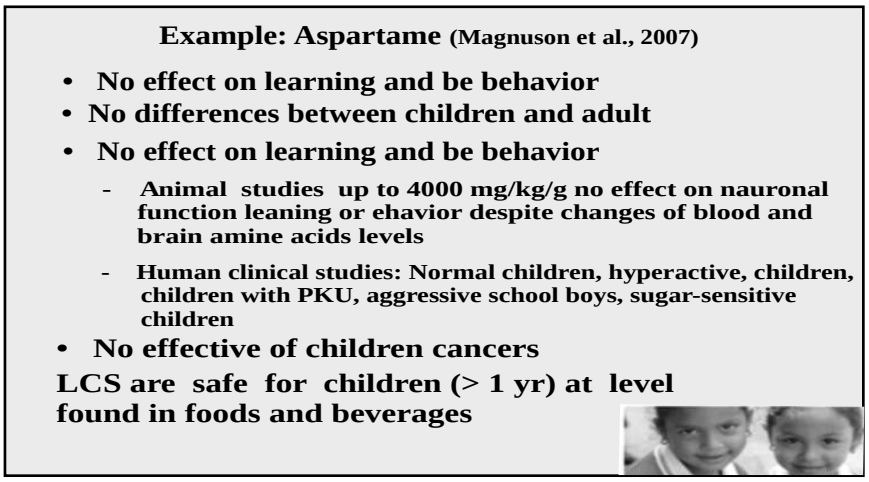
Use of LCS in Children

Toxicological protocols adopted for LCS cover all periods of rapid growth and development maturation and aging and therefore all circumstances of human exposure are covered. Exposure during the juvenile period is taken into account and so the ADI does apply to children as well.

Studies have indicated that there is no difference in the metabolism of aspartame between children and adult; there is no effect on learning and behaviour (Magnuson, 2007). Animal studies have indicated that doses up to 4000 mg/kg/d, produce no effect on neuronal function, learning or behavior despite changes in blood and brain amino acids levels. Human clinical studies have been carried out on various groups: normal children, hyperactive children, children with PKU, aggressive school boys and sugar-sensitive children. All these studies show no effect on childhood cancers.

Thus it can be said that LCS are safe for children (>1 yr.) at levels found in foods and beverages.

Figure 3. Safety of Products Containing LCS for Consumption by Children



Source: Presentation by Dr. Bernadene Magnuson, Academy of Toxicological Sciences

LCS and Use in Pregnancy and Lactation

The ADI's (as discussed previously) have been derived at by keeping into account all ages and different physiological conditions, before approval thus, it has been determined by the US FDA, JECFA etc. that the use of LCS is safe for all populations, including special groups like the children, pregnant and lactating women and the elderly. During pregnancy, especially during gestational diabetes, there is a need to curb excess weight gain. This can be safely done through the use of LCS and they can continue to consume other more nutritious foods to balance out the calorie intake.

LCS and Cancer

There have been a few claims that aspartame (Soffritti et al., 2006, 2007; Bosetti et al, 2009) and sucralose (Soffritti et al., 2016) reported increased incidence of some cancers. However, these may be due to lack of understanding of the biological fate of LCS after their ingestion. Aspartame for example, gets digested to aspartic acid and phenylaline. Both aspartic acid and phenylaline are also found naturally in many other commonly consumed food products like milk, orange juice etc. Hence, the fact that aspartame metabolises into the same by products which some other food products metabolise into clearly indicates that these LCS are safe.

Table 4. Dietary Sources of Aspartame Digestion Products

Food	Phenylalanine (mg)	Aspartic acid (mg)	Methanol (mg)
Aspartame-Sweetened Soft Drink (340 ml)	90	72	18
Non-Fat Milk (340 ml)	606	953	-
Tomato Juice (340 ml)	58	346	107
Orange Juice (340 ml)	24	180	23

Source: Presentation by Dr. Bernadene Magnuson, Academy of Toxicological Sciences

To further find out the truth about these claims of linkage between LCS and cancer, an extensive review was conducted by EFSA in 2006 and in 2013; Agence Franciase de Securite Santarie des Aliments (2006); U.S. National Toxicology Program; FDA, Health Canada; Expert Panel (Critical Review in Toxicology, 2007). All agreed that:

- there is no credible evidence that aspartame is carcinogenic.
- no need to further review the safety of aspartame.
- no need to revise previously established ADI.

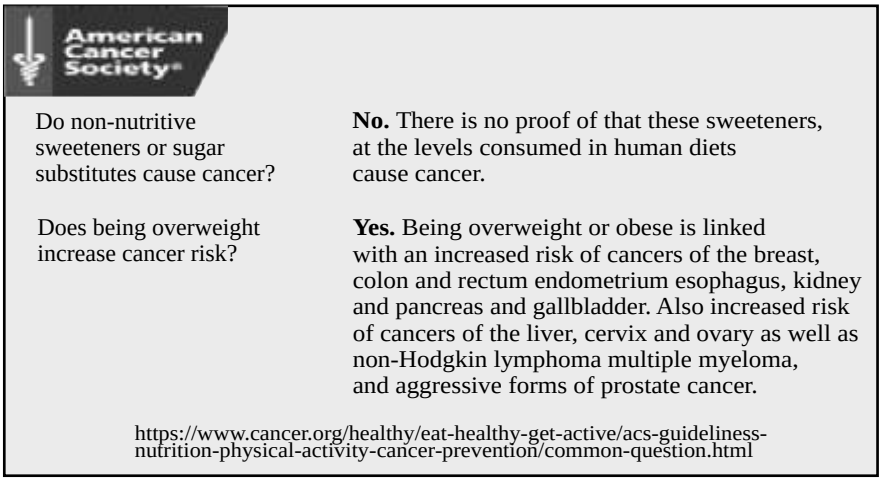
In fact, the American Cancer Society has stated that rather than LCS, being overweight is a strong risk factor in developing cancer. When consumption of LCS leads to intake of lower calories and reductions in overweight/obesitythis will result in lower cancer risk.

Table 5. Studies on Association Between LCS & Cancer

Epidemiological studies find no association between LCS and Cancer			
Author	**Type of study (N)**	**Consumption**	**Conclusions**
Gurney (1997)	**56 brain tumor cases 94 controls**	**Dietary recall - Personal interview**	**No association**
Hardell (2001)	**30 brain tumor cases 45 controls**	**Recall of low-calorie soft drinks**	**No association**
Bunin (2005)	**315 child brain tumor cases, 315 controls**	**Food frequency by mothers**	**No association**
Lim (2006)	**Prospective 473,984 subjects, 5 yr. Hematopoietic and brain cancers**	**Food frequency questionnaires**	**No associations**
Gallus (2007)	**Case control; various cancers (8976 cases, 7028 controls)**	**Food frequency questionnaires**	**No association**
Bosetti (2009)	**Case control; various cancers (1010 cases, 2107 controls)**	**Food frequency questionnaires**	**No association**
Schernhammer (2012)	**Prospective: 22 yr. Nurses' Health (77,218 F); Health Professionals (47,810 M). Hematopoietic cancers**	**Food frequency questionnaires every 4 years**	**No association when combined cohorts. Weak positive with separate**
McCullough (2014)	**Prospective: 10 yr. Cancer Prevention cohort; (100,442 M&F) Non-Hodgkin lymphoma**	**Food frequency questionnaires every 2 years**	**No association** with aspartame or diet beverage consumption

Source: Presentation by Dr. Bernadene Magnuson,Academy of Toxicological Sciences

Figure 4. Statement by American Cancer Society on LCS & Cancer

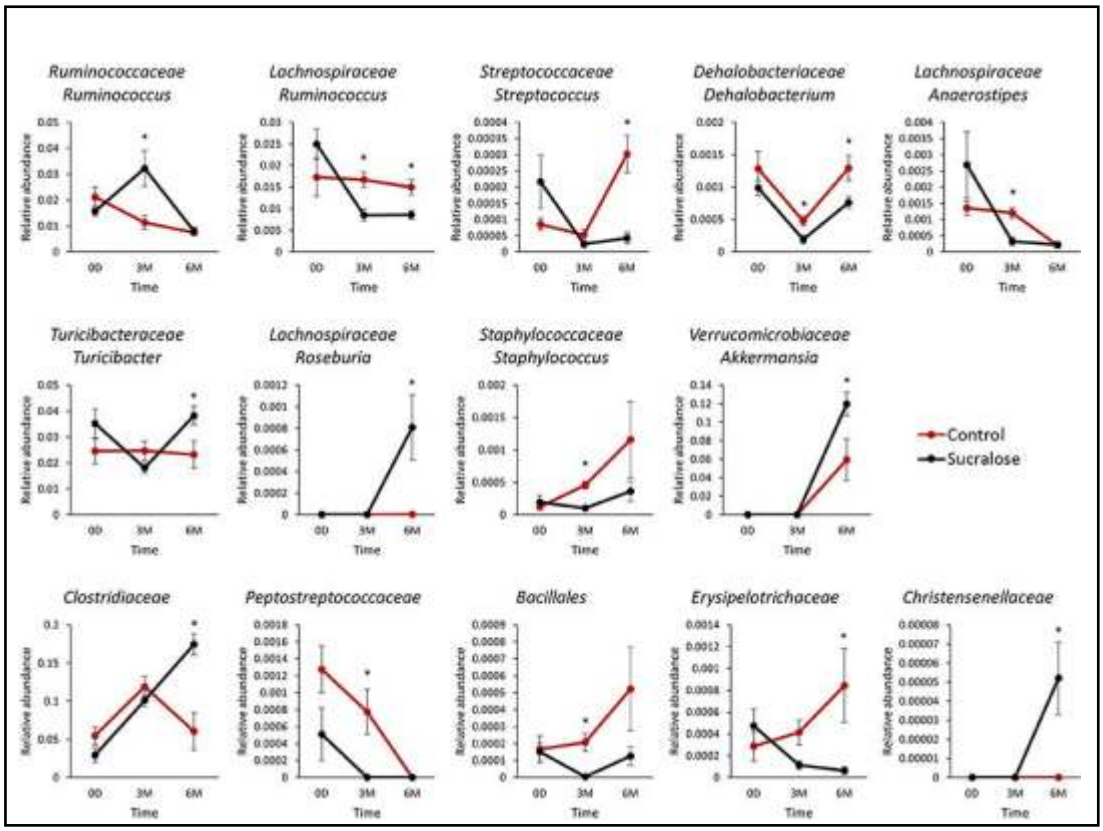


Source: Presentation by Dr. Bernadene Magnuson, Academy of Toxicological Sciences

LCS and Gut Microbiota

A research paper concluded that LCS alteres the gut microbiota (Suez et al 2014). It was claimed that sucralose affects gut microflora and may cause liver inflammation in mice. In order to find out the validity of this claim, studies were carried out. Sucralose was fed at high doses to test animals. It was found that, changes in microflora in control group were similar to treatment group (Bian et al, 2017). This confirmed well conducted previous toxicology studies showing no effect on any parameter when sucralose was fed at high doses for life. (Magnuson et al., 2017).

Graph 1. Microflora in Control Group vis-à-vis Sucralose Group



Source: Presentation by Dr. Bernadene Magnuson,Academy of Toxicological Sciences

Note: Microflora in Control group changes as much as sucralose group. There is no consistent effect.

Well conducted studies thus provide no evidence of adverse effects of LCS due to alterations in the gut microbiota. The low amounts of LCS consumed and their biological fate make it unlikely that LCS significantly affect the gut microbiome. (Goodrich et al, 2014; Russel et al, 2016).

LCS and Insulin Resistance

In connection with LCS and gut microbiota, a few studies also indicated a higher levels of HbA1C among users of high amounts of LCS. An alteration in gut bacteria was thought to be responsible for this (Suez et al, 2014). Another study, which was done on rats, using aspartame, also found an increased risk of glucose intolerance. Test animals had raised levels of propionate—short-chain fatty acids (SCFAs) involved in sugar production. Consumption of LCS shifted gut microbiota to produce propionate, which generated higher blood sugar levels (Palmnas et al, PLOS One, 2014).

However, again these claims have been refuted and Position Statements acknowledge potential benefit of use of LCS as substitute for caloric sweeteners for management of blood glucose in individuals with diabetes. (ADA, 2017).

Thus, LCS may be in fact a good alternative to sugar in diabetes. Unlike sugar, artificial sweeteners generally don't raise blood sugar levels because they are not carbohydrates. They help LCS in curbing the sweet craving and provide greater flexibility in meeting dietary goals.

LCS and Appetite or Hunger

It has been said that LCS increase the consumption of calories rather than getting the calorie intake down. The human brain responds to sweetness (provided by the LCS) with signals to eat more and the body expects a surge in glucose (which does not happen in case of LCS). When this expectation is not met, the body continues to crave sweets. This is the basis on which a few studies carried out have indicated that LCS in fact increase the calorie consumption and thereby lead to weight gain rather than weight loss (Wang et al., 2006, 2017; Park et al., 2017).

Most human studies and clinical reviews have however, concluded that LCS do not affect appetite or hunger or desire for sweetness. Randomized Control Trials (RCT) that measured hunger and food choices demonstrate either no or possible overall beneficial effect (Anderson et al. 1989; Drewnowski et al., 1994, Rogers et al. 1995; Blackburn et al.. 1997; Mattes et al.. 2009; Anderson et al. 2012; Gardner et al., 2012; Piernas et al., 2013, Peters et al., 2016). Most of these studies reported no effect on gut hormones, no adverse effect on functions related to gut hormones including blood glucose and insulin levels, appetite and gastric emptying.

Thus, it has been revealed that there is no adverse effect of LCS use with respect to hunger and appetite in healthy individuals and individuals with diabetes (Bryant & McLaughlin, 2016; Meyer-Gerspach et al., 2016, Magnuson et al., 2017).

In fact studies also reveal that even when Type 1 diabetic children (aged 4-18) consumed LCS liberally, there are little chance for them to exceed ADIs for acesulfame-k, aspartame, neohesperidin, sucralose, saccharin, steviol glycosides and neotame. An alteration between different food and beverage products containing different LCS reduces chances of exceeding the ADI (Dewinter et al, 2016).

Study finds little change for T1D children to exceed LCS ADIs

Children with type 1 diabetes (4-18 yr)
- **food frequency questionnaire**
- **tier to (maximum concentration) an tier 3(maximum used concentrations) method of exposure assessment used.**

Conclude: "..little chance for T1D children to exceed ADIs for acesulfame-k, aspartame, neohesperidin, sucralose, saccharin, stevial glycosides and neotame."

Alternation between different food and beverage products containing different LCS reduces

Dewinter et al. (2016)
Food Additives & contam. v33

Source: Presentation by Dr. Bernadene Magnuson, Academy of Toxicological Sciences

LCS and Weight Management

LCS replace the sugar in a food and thereby reduce the calories, especially in beverages. But, it has been claimed that consumption of low-calorie sweeteners may confuse the relationship between sweet taste and calories (and thereby increase sugar and energy intake); increase desire for sweetness (and thereby increase sugar and energy intake) or cause consumers to consciously over-compensate for the 'calories saved'. However, by replacing all or some sugar, low-calorie sweeteners reduce the energy content of foods and especially drinks –leading to reduced energy intake and body weight.

No evidence has been found regarding LCS and increases in sugar and energy intake in both animal and human studies. In fact, in the short-term, exposure to a sweet drink decreases desire and intake of sweet food (Piernas et al, 2013). No evidence has been found in connection with conscious over-compensation for the 'calories saved' by consuming LCS (Rogers et al, 2016).

Studies have indicated that sugar in a food is just a predictor of sweetness and not its energy content. In fact most of the commonly consumed high carbohydrate foods like grains are energy dense foods but not sweet. On the other hand fruits like berries which are sweet do not have high energy content.

Table 6. Association Between Sugar Content & Energy Content of Natural Foods

Energy, sugar and total carbohydrate content per 100 g of some 'natural' (i.e., minimally processed) carbohydrate-rich foods

	Energy, kcal	Sugar, g	Total CHO, g
Fresh fruits and berries, n=7	58	10.3	14.4
Roots and tubers, n=8	78	3.1	17.9
Grains, n=4	121	1.0	25.2

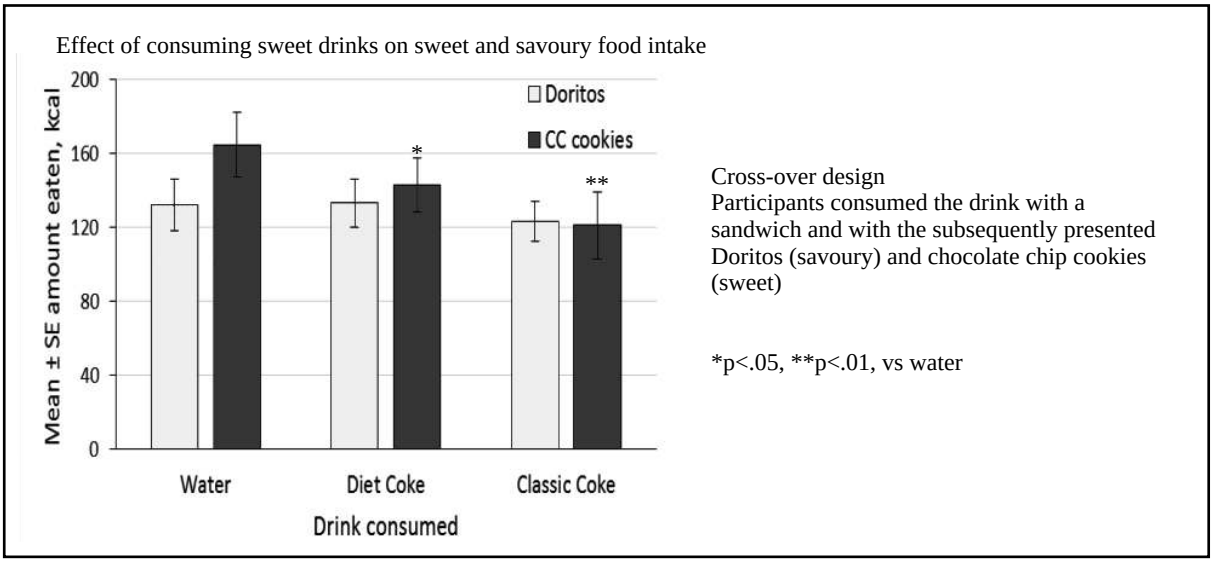
Some individual fruits, per 100 g

Strawberry = 5 g sugar, 33 kcal
Blueberry = 10 g sugar, 57 kcal
Grape = 16 g sugar, 67 kcal

Source: Presentation by Prof. Peter Rogers, University of Bristol

Note: Sugar content does not predict the energy content of 'natural' foods

Figure 5. Association Between Consumption of LCS & Impact on Desire for Sweeteners



Source: Presentation by Prof. Peter Rogers, University of Bristol

Appendix I

JECFAEvaluation of Intense Sweeteners(LCS)

Intense Sweeteners	INS	ADI	Year
Acesulfame potassium	950	0-15 mg/ kg bw	1990
Advantame	969	0-5 mg/kg bw	2013
Aspartame	951	0-40 mg/kg bw	1981
Aspartame-Acesulfame potassium	962	0-40-mg/kg bw; 0-15 mg/kg bw	2000
Alitame	956	0-1 mg/kg bw	1996
Cyclamate, Calcium	952 (iii)	0-11 mg/kg bw	1982
Cyclamate, Sodium	952 (iv)	0-11 mg/kg bw	1982
Cyclamic acid	952 (i)	0-11 mg/kg bw	2009
Neotame	961	0-2 mg/kg bw	2003
Saccharin	954	0-5- mg/kg bw	1993
Saccharin, Calcium	954(ii)	0-5 mg/kg bw	1993
Saccharin, Potassium	954 (iii)	0-5 mg/kg bw	1993
Saccharin, Sodium	954 (iv)	0-5 mg/kg bw	1993
Sucralose	955	0-15 mg/kg bw	1990
Steviol glycosides	960	0-4 mg/kg bw	2008
Thaumatin	957	Not specified	1985

Source: Presentation by Dr. Ashley Roberts, Intertek

Appendix II

Sweetness and Calories Associated With Low Calorie High Intensity Sweeteners (HIS)

INS	Name	Sweetness*	Calories (kcal/g)
950	Acesulfame K	130 – 200	0
951	Aspartame	200	4
952	Cyclamate	30 – 50	0
954	Saccharin	300 – 500	0
955	Sucralose	600	0
956	Alitame	2000	1.4
957	Thaumatin	2000 – 3000	4
960	Steviol glycosides	200 – 300	0
961	Neotame	8000	0

* Comparative value when sweetness of sucrose is 1.

- Sweetness: many times sweeter than sucrose (30 to 8000)
- Calories: practically no calorie
- Have properties that contribute to sensory characteristics of food

Source: Food and Sweeteners (Korin Book, 2008); Sweeteners facts (Calorie Control Council); Alternative sweeteners (Lyn O'Brien Nabors, 2001)

REFERENCES

1. NNMB Technical Report No. 27 Diet and Nutritional Status of Urban Population in India and Prevalence of Obesity, Hypertension, Diabetes and Hyperlipidemia in Urban Men and Women.
2. ILSI-India Monograph on Low Calorie / Non Nutritive Sweeteners: Safety and Benefits.
3. ILSI-India Monograph on Role of Diet, Physical Activity & Lifestyle in Promoting Health.
4. Erickson J, Slavin J. Total, Added, and Free Sugars: Are Restrictive Guidelines Science-Based or Achievable? Nutrients 2015, 7, 2866-2878.
5. FSSAI, Report of the Expert Group on consumption of fat, sugar and salt and its health effect on the Indian population, 2017.
6. Gulati S, Misra A. Sugar Intake, Obesity, and Diabetes in India. Nutrients 2014, 6, 5955-5974.
7. KPMG. The Indian Sugar Industry: Sector Roadmap 2017, June 2007.
8. Barry M Popkin Linda S Adair Shu Wen Ng. Global nutrition transition and the pandemic of obesity in developing countries. Nutrition Reviews 2012, 70, 1: 3–21.
9. World Health Organization. Report of the Commission on ending childhood obesity, Geneva: 2016.
10. https://www.kenresearch.com/blog/2016/03/revenues-sugar-industry-projected-increase-inr-1033-billion-fy2020-ken-research/ accessed 2.9.2017
11. Kinra S, Bowen LJ, Lyngdoh T, et al. Socio-demographic patterning of non-communicable disease risk factors in rural India: a cross sectional study. BMJ 2010; 341:c4974.
12. World Health Organisation Noncommunicable diseases Available from: http://www.who.int/topics/noncommunicable_diseases/en/ (Accessed on 27 Jan 2016).
13. Fuster V, Kelly BB, Vedanthan R. Promoting Global Cardiovascular Health Moving Forward. Circulation 2011; 123(15): 1671-8.
14. Sarrafzadegan N, Baghaei A, Sadri G, et al. Isfahan healthy heart program: Evaluation of comprehensive, community-based interventions for non-communicable disease prevention. Prev Control 2006; 2(2):73-84.
15. World Health Organization Guideline: Sugars intake for adults and children. Geneva; 2015 Available on: http://apps.who.int/iris/bitstream/10665/149782/1/9789241549028_eng.pdf (Accessed 11 Feb 2016).
16. Food and Agriculture Organization Food safety and quality: Chemical risks and JECFA. Available at: http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/ (Accessed 11 Mar 2016).
17. WHO, 2009a
    WHO (2009). Principles and Methods for the Risk Assessment of Chemicals in Food. (Environmental Health Criteria, no 240). Rome, Italy: Food and Agriculture Organization of the United Nations (FAO) / Geneva, Switz.: World Health Organization (WHO) / International Programme on Chemical Safety (IPCS). Available at: http://www.who.int/foodsafety/publications/chemical-food/en/.
18. WHO, 2009b
    FAO/WHO (2009). Chapter 6: Dietary exposure assessment of chemicals in food. In: Principles and Methods for the Risk Assessment of Chemicals in Food. (Environmental Health Criteria, no 240). Geneva, Switz.: World Health Organization (WHO) / International Programme on Chemical Safety (IPCS). Available at: http://whqlibdoc.who.int/ehc/WHO_EHC_240_9_eng_Chapter6.pdf.
19. Soffritti et al., 2005
    Soffritti M, Belpoggi F, Esposti DD, Lambertini L (2005). Aspartame induces lymphomas and leukaemias in rats. Eur J Oncol 10(2):107-116.

20. Soffritti et al., 2010
Soffritti M, Belpoggi F, Manservigi M, Tibaldi E, Lauriola M, Falcioni L, et al. (2010). Aspartame administered in feed, beginning prenatally through life span, induces cancers of the liver and lung in male Swiss mice. Am J Ind Med 53(12):1197-1206. DOI:10.1002/ajim.20896.

21. Soffritti et al., 2016
Soffritti M, Padovani M, Tibaldi E, Falconi L, Manservisi F, Lauriola M, Bua, L. et al. (2016). Sucralose administered in feed beginning prenatally through lifespan, induces hematopoietic neoplasias in male Swiss mice. Int J Occup Environ Health 22(1):7-17. DOI:10.1080/10773525.2015.1106075.

22. Suez et al., 2015
Suez J, Korem T, Zilberman-Schapira G, Segal E, Elinav E (2015). Non-caloric artificial sweeteners and the microbiome: findings and challenges. Gut Microbes 6(2):149-155. DOI:10.1080/19490976.2015.1017700.

23. American Cancer Society. https://www.cancer.org/healthy/eat-healthy-get-active/acs-guidelines-nutrition-physical-activity-cancer-prevention/common-questions.html

24. Berry C, Brusick D, Cohen SM, Hardisty JF, Grotz VL, Williams GM. 2016. Sucralose non-carcinogenicity: a review of the scientific and regulatory rationale. Nutr Cancer. 68:1247-1261.

25. Bian X, Chi L, Gao B, Tu P, Ru H, Lu K. Gut Microbiome Response to Sucralose and Its Potential Role in Inducing Liver Inflammation in Mice. Front Physiol. 2017 Jul 24;8:487.

26. Bosetti C, Gallus S, Talamini R, Montella M, Franceschi S, Negri E, La Vecchia C. Artificial sweeteners and the risk of gastric, pancreatic, and endometrial cancers in Italy. Cancer Epidemiol Biomarkers Prev. 2009 Aug;18(8):2235-8. http://cebp.aacrjournals.org/content/18/8/2235.abstract.

27. Bunin, GR, Kushi, LH, Gallagher, PR, Rorke-Adams, LB, McBride, ML, and Cnaan, A. Maternal diet during pregnancy and its association with medulloblastoma in children: a children's oncology group study (United States). Cancer Causes Control 2005;16 (7):877–91. http://www.ncbi.nlm.nih.gov/pubmed/16132798.

28. Carakostas MC, Curry LL, Boileau AC, Brusick DJ. Overview: the history, technical function and safety of rebaudioside A, a naturally occurring steviol glycoside, for use in food and beverages. Food Chem Toxicol. 2008 Jul;46 Suppl 7:S1-S10.

29. Dewinter L, Casteels K, Corthouts K, Van de Kerckhove K, Van der Vaerent K, Vanmeerbeeck K, Matthys C. Dietary intake of non-nutritive sweeteners in type 1 diabetes mellitus children. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2016;33(1):19-26.

30. [EFSA] European Food Safety Authority. 2006. Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to a new long-term carcinogenicity study on aspartame. EFSA J. 356:1-44. doi:10.2903/j.efsa.2006.356. [Internet]. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/356.

31. [EFSA] European Food Safety Authority. 2011. EFSA Statement on the scientific evaluation of two studies related to the safety of artificial sweeteners. EFSA J. 9(2): 2089 [16 pp.]. doi:10.2903/j.efsa.2011.2089. [Internet]. [Cited 2017 Jan 20]. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/2089.

32. European Food Safety Authority. Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive. EFSA J. 2013;11:3496. doi:10.2903/j.efsa.2013.3496.

33. EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food, 2017. *Statement on the validity of the conclusions of a mouse carcinogenicity study on sucralose (E 955) performed by the Ramazzini Institute. EFSA Journal 2017;15(5):4784, 14 pp.* https://doi.org/10.2903/j.efsa.2017.4784.

34. Gallus S, Scotti L, Negri E, Talamini R, Franceschi S, Montella M, Giacosa A, Dal Maso L, La Vecchia C. Artificial sweeteners and cancer risk in a network of case-control studies. Ann Oncol. 2007 Jan;18(1):40-4. http://www.ncbi.nlm.nih.gov/pubmed?term=17043096.

35. Gardner C, Wylie-Rosett J, Gidding SS, Steffen LM, Johnson RK, Reader D, Lichtenstein AH; Nonnutritive sweeteners: current use and health perspectives: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation. 2012 Jul 24;126(4):509-19.

36. Gift JS, Caldwell JC, Jinot J, Evans MV, Cote I, Vandenberg JJ. 2013. Scientific considerations for evaluating cancer bioassays conducted by the Ramazzini Institute. Environ Health Perspect. 121:1253-1263.

37. Goodrich JK, Di Rienzi SC, Poole AC, Koren O, Walters WA, Caporaso JG, Knight R, Ley RE. Conducting a microbiome study. Cell. 2014 Jul 17;158(2):250-62.

38. Grice HC, Goldsmith LA. Sucralose--an overview of the toxicity data. Food Chem Toxicol. 2000;38 Suppl 2:S1-6.

39. Grotz VL, Munro IC. An overview of the safety of sucralose. Regul Toxicol Pharmacol. 2009 Oct;55(1):1-5.

40. Gurney JG, Pogoda JM, Holly EA, Hecht SS, Preston-Martin S. Aspartame consumption in relation to childhood brain tumor risk: results from a case-control study. J Natl Cancer Inst. 1997 Jul 16;89(14):1072-4. Erratum in: J Natl Cancer Inst 1997 Oct 1;89(19):1460. http://jnci.oxfordjournals.org/content/89/14/1072.full.

41. Hayes AW, Dayan AD, Hall WC, Kodell RL, Williams GM, Waddell WD, Slesinski RS, Kruger CL. 2011. A review of mammalian carcinogenicity study design and potential effects of alternate test procedures on the safety evaluation of food ingredients. Regul Toxicol Pharmacol. 59:142-175.

42. Hardell L, Mild KH, Påhlson A, Hallquist A. Ionizing radiation, cellular telephones and the risk for brain tumours. Eur J Cancer Prev. 2001 Dec;10(6):523-9. http://www.ncbi.nlm.nih.gov/pubmed/11916351. Accessed July 3, 2012

43. Health Canada. Health Canada Comments on the Recent Study Relating to the Safety of Aspartame. May 5, 2006. http://www.hc-sc.gc.ca/fn-an/securit/addit/sweeten-edulcor/aspartame_statement-eng.php. Accessed July 3, 2012.

44. JECFA monographs on toxicology studies of food ingredients. http://www.who.int/foodsafety/publications/monographs/en/

45. Lim U, Subar AF, Mouw T, Hartge P, Morton LM, Stolzenberg-Solomon R, Campbell D, Hollenbeck AR, Schatzkin A. Consumption of aspartame-containing beverages and incidence of hematopoietic and brain malignancies. Cancer Epidemiol Biomarkers Prev. 2006 Sep;15(9):1654-9. http://www.ncbi.nlm.nih.gov/pubmed?term=16985027

46. Magnuson BA, Burdock GA, Doull J, Kroes RM, Marsh GM, Pariza MW, Spencer PS, Waddell WJ, Walker R, Williams GM. Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. Crit Rev Toxicol. 2007;37(8):629-727.

47. Magnuson BA, *Carakostas MC*, Moore NH, Poulos SP, Renwick AG, Biological Fate of Low Calorie Sweeteners. Nutrtion Reviews. 2016 Vol. 74(11):670–689

48. McCullough ML, Teras LR, Shah R, Diver WR, Gaudet MM, Gapstur SM. Artificially and sugar-sweetened carbonated beverage consumption is not associated with risk of lymphoid neoplasms in older men and women. J Nutr. 2014 Dec; 144(12):2041-9.

49. Schernhammer ES, Bertrand KA, Birmann BM, Sampson L, Willett WC, 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 Dec; 96(6):1419-28. doi: 10.3945/ajcn.111.030833. Epub 2012 Oct 24. Erratum in: Am J Clin Nutr. 2013 Aug; 98(2):512.

50. Schoeb TR, McConnell EE. Commentary: further comments on Mycoplasma pulmonis and lymphoma in bioassays of rats. Vet Pathol. 2011 Mar;48(2):420-6.

51. Schoeb TR, McConnell EE, Juliana MM, Davis JK, Davidson MK, Lindsey JR. Mycoplasma pulmonis and lymphoma in bioassays in rats. Vet Pathol. 2009 Sep;46(5):952-9.

52. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, Abrouk M, Farahnik B, Nakamura M, Zhu TH, Bhutani T, Liao W. Influence of diet on the gut microbiome and implications for human health. J Transl Med. 2017 Apr 8;15(1):73.

53. Soffriti M, Belpoggi F, Degli Esposti D, Lambertini L, Tibaldi E, Rigano A. 2006. First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. Environ Health Perspect 114:379–385.

54. Soffritti M, Belpoggi F, Tibaldi E, Degli Esposti D, Lauriola M. 2007. Life-span exposure to low doses of aspartame beginning during prenatal life increases cancer effects in rats. Environ Health Perspect 115:1293–1297.

55. Soffritti M, Padovani M, Tibaldi E, Falconi L, Manservisi F, Lauriola M Bua L, Manservigi M, Belpoggi F. 2016. Sucralose administered in feed beginning prenatally through lifespan, induces hematopoietic neoplasias in male Swiss mice. Int J Occup Environ Health. 22:7-17.

56. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, Israeli D, Zmora N, Gilad S, Weinberger A, Kuperman Y, Harmelin A, Kolodkin-Gal I, Shapiro H, Halpern Z, Segal E, Elinav E. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature. 2014 Oct 9;514(7521):181-6.

57. US Food and Drug Administration FDA statement on European aspartame study Washington, DC http://www.fda.gov/Food/IngredientsPackagingLabeling/ FoodAdditivesIngredients/ucm208580.htm. Published May 8, 2006

58. [US EPA] U.S. Environmental Protection Agency. 2012. Update on Ramazzini Institute data in IRIS assessments [Internet]. Washington (DC): U.S. Environmental Protection Agency (US EPA) [cited 2017 Jan 20]. Available from: https://www.epa.gov/iris/update-ramazzini-institute-data-iris-assessments [Mar. 8, 2012].

59. International Diabetes Federation. Unwin N, Whiting D, Gan D, Jacqmain O, Ghyoot G, editors. IDF diabetes atlas. 4th ed. Belgium: International Diabetes Federation; 2009. p. 12.

60. Radha V, Vimaleswaran KS, Babu HNS, Abate N, Chandalia M, Satija P, et al. Role of genetic polymorphism peroxisome proliferator – Activated Receptor – 2 Pro 12Ala on ethnic susceptibility to diabetes in south Asian and Caucasian subjects (CURES - 5). Diabetes Care 2006; 29: 1046-51.

61. Mohan V, Deepa M, Deepa R, Shanthirani CS, Farooq S, Ganesan A, et al. Secular trends in the prevalence of diabetes and impaired glucose tolerance in urban south India – the Chennai Urban Rural Epidemiology Study (CURES-17). Diabetologia 2006; 49: 1175-8.

62. Mohan V, Radhika G, Sathya RM, Tamil SR, Ganesan A, Sudha V. Dietary carbohydrates, glycaemic load, food groups and newly detected type 2 diabetes among urban Asian Indian population in Chennai, India (Chennai Urban Rural Epidemiology Study 59). Br J Nutr 2009; 102: 1498-506.

63. ADA, 2017 http://www.sweeteners.org/category/5/research/214/adas-2017-guidelinessupport-thebeneficial-role-of-low-calorie-sweeteners-indiabetesmanagement;
European Food Safety Authority (EFSA) (http://www.sweeteners.org/category /38/benefits/50/benefits-forpeople-with-diabetes).

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